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MYOCARDIAL ISCHEMIA AND PERIOPERATIVE INFARCTION

J. G. Reves, MD, *Guest Editor*

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ERRATUM

In the March 1988 issue, the affiliations of the authors of "Metabolic Effects of the Neuroendocrine Stress Response" were incorrectly listed. The correct affiliations follow.

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The development of myocardial ischemia and infarction continues to be a serious public health problem in this country. Careful management of the determinants of myocardial oxygen supply and demand prevents many perioperative episodes of myocardial ischemia; however, despite optimal management of these parameters, ischemia is still noted to occur. Traditional investigative research has sought to explain these findings primarily on the basis of atherosclerotic coronary artery disease or coronary vasospasm. Recently, newer concepts such as unstable and mixed angina, silent myocardial ischemia, reperfusion injury, and the role of platelets and prostaglandins have emerged, which have broadened our understanding of the mechanisms of myocardial ischemia and infarction.

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John H. Tinker

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Carol Lee Lake

Ischemia occurs in 11 to 38 per cent of patients undergoing cardiac surgery. Like ischemia, myocardial infarction has a wide range of incidence varying from 2 to 10 per cent. Despite the use of sophisticated monitors, some perioperative ischemia is undetected or "silent." Factors associated with perioperative ischemia include hemodynamic changes causing imbalance between myocardial oxygen supply and demand, coronary air embolism, and technical problems during attempted revascularization. Measures used to alleviate ischemia and prevent infarction include control of oxygen supply/demand balance with vasodilator and anesthetic drugs, swift and complete coronary revascularization, and control of timing, pressure, and composition of reperfusion solutions.

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The occurrence of myocardial ischemia in the perioperative period is influenced by many factors including patient characteristics, the severity of coronary artery disease, medical treatment, the nature of the surgical procedure, and the anesthetic management. Recent improvements in the specificity and sensitivity of ischemia detection are leading to greater precision in risk identification and classification. Successful treatment and prevention of myocardial infarction depends on the early diagnosis of ischemia. The use of therapeutic interventions that have been shown to be efficacious in patients with unstable angina, myocardial infarction, and those undergoing coronary artery revascularization may reduce the incidence of postoperative myocardial infarction.

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these now include simultaneous display of multiple ECG leads, automated on-line ST analysis, and the new technology of transesophageal two-dimensional echocardiography. It is the intent of this article to bring the reader up to date with the theory, value, and practical use of these newer modalities.

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Reperfusion treatment has become standard treatment during acute myocardial infarction over the last several years. Currently, intravenous thrombolytic agents (streptokinase, tPA, and, on some occasions, urokinase) are widely used for this purpose. These agents have been shown to be effective in achieving reperfusion. The alternative method to achieve reperfusion is percutaneous transluminal coronary angioplasty (PTCA). PTCA has been shown to be an effective method of establishing reperfusion during acute myocardial infarction and decreasing residual stenosis. Many studies have demonstrated significant salvage of myocardium by reperfusion therapy and recovery of left ventricular function in the infarct segment. In addition, recent randomized studies have clearly demonstrated beneficial effects on prognosis following thrombolytic therapy. In-hospital mortality as well as long-term mortality were remarkably reduced with intravenous thrombolytic therapy.

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Preface

The American Heart Association estimates that 5 million people have symptomatic ischemic heart disease, and it has recently been calculated that as many as 7 to 10 million people in the United States are at risk for morbid or mortal outcomes due to coronary artery disease.[1] Ischemic heart disease is the leading cause of death in this country, and with an aging population the number of people with pathologically significant coronary artery disease is increasing. Although the precise number of patients with important ischemic heart disease requiring surgery is not known, London and Mangano have estimated that it is a large proportion of our patients. They have, in fact, done the following calculation to estimate the surgical population at risk for coronary artery disease: assuming an average prevalence rate of 10 per cent in the over 65 age group and a 5 per cent rate in the 45 to 65 age group, close to 1 million of the 12 million surgical patients in the over 45 age group are at risk of having ischemic heart disease. Thus, by the patient volume alone, the topic of ischemic heart disease and anesthesia is significant.

However, the importance of ischemic heart disease, surgery, and anesthesia is far more than the large number of patients that constitute this subgroup of our daily practice: the true significance of this group is that they present formidable patient management problems since they have ischemia, infarction, and death in the perioperative period. It is for this reason that this volume has been written.

In this issue the causes and mechanisms of acute ischemia and infarction are described. It is clear that the age-old concept of avoid hypotension and hypoxia is not adequate for our understanding of the causes of ischemia and infarction. The laboratory models used for helping us understand through basic science investigations and clinical studies are presented and critiqued. It is clear that we can create in the laboratory some relevance to clinical practice experiments, but that no laboratory experiment approximates exactly what we face in our everyday practice: thus coronary steal with isoflurane in the dog does not necessarily mean ischemia in man anesthetized with isoflurane. Fortunately, many laboratory studies do explain clinical events.

This issue reviews methods of detecting myocardial ischemia and infarction including the newer approaches with regional wall motion abnormalities using transesophageal echocardiography. The incidence of ischemia and its consequences are discussed in both cardiac and noncardiac surgery. The distinction between these two patient populations must be made because the postoperative period is potentially different and thus causes of infarction differ between groups. In coronary artery surgery infarction can occur in the absence of prebypass ischemia. Postoperative ischemia and infarction are less likely to occur in cardiac surgical patients because the heart is revascularized during cardiac surgery. Whereas infarction is most likely to occur intraoperatively in cardiac surgery, it is most likely to occur postoperatively in noncardiac surgical patients.

The prevention and treatment of myocardial ischemia is dealt with in three of the articles. Principles of myocardial protection involve the maintenance of adequate cardiac metabolic substrates and reduction of their use. A great variety of drugs including anesthetics are used for this purpose preoperatively, intraoperatively, and postoperatively. Indeed, prevention of ischemia depends on *supplementing* with anesthesia the antianginal drugs that patients routinely take. Anesthesia, per se, should be viewed as a myocardial protective measure[2] since it has been shown by many that ischemia is less likely to occur intraoperatively than preoperatively and postoperatively in patients at risk of developing ischemia. Prompt treatment of ischemia, should it occur, is obviously required to prevent the progression of ischemia to arrhythmia, pump failure, infarction, and death. If infarction does occur in noncardiac surgical patients there are now medical interventional strategies that can be rapidly employed. There is no report of the experience of this medical interventional practice in the postoperative patient, but it might reduce the extraordinary mortality (50 per cent) in this subset of noncardiac surgical patients.

Despite the information contained in this issue there are areas of interest and unknown areas that have not yet been covered. The reader is referred to the review of the assessment of cardiac risk including tests that identify the highest risk patient.[1] Why does ischemia occur in about 50 per cent of cardiac and noncardiac surgical patients without hemodynamic evidence of imbalance in myocardial oxygen supply and demand? Why do the majority (>90 per cent) of intraoperative ischemic episodes *not* lead to postoperative infarction? (Is it because of the protective effect of anesthesia and the prompt therapy?) Why do noncardiac surgical patients have the highest incidence of infarction in the first 3 postoperative days, and can this incidence and its mortality be reduced? How will better risk identification with Holter monitoring and other diagnostic studies (for example, dipyridamole thallium testing) alter our approach to these high-risk patients, and will we be able to reduce the incidence of infarction and death? These and many other questions remain regarding the management of the patient with ischemic heart disease. This issue is an attempt to compile the latest information with the older concepts in a way that is useful to the clinician and stimulating to the researcher in this rapidly changing and extremely important field of our everyday practice of anesthesia.

I am indebted to the contributors for their incisive treatment of their topics and for the timeliness of their submissions. It is hoped that the material herein is helpful to the reader who in a busy practice must care for many patients with ischemic heart disease.

J. G. Reves, MD
Guest Editor

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Foreword

This issue on "Myocardial Ischemia and Perioperative Infarction" is both quite timely and of much significance. Moreover, its contents are of broad interest to physicians and surgeons alike. The editor has assembled a formidable group of contributors, each well-recognized authorities in the fields covered in this authoritative and completely updated review.

Since the report by Wilson in 1912 of a patient who died of coronary occlusion on the first postoperative day following gastroenterostomy for a duodenal ulcer, physicians and surgeons alike have had a committed interest in preoperative detection of high-risk candidates as well as of means of preventing myocardial infarction either in the perioperative or postoperative course. In 1970, my colleagues and I studied a group of patients undergoing surgical procedures, each of whom had an abnormal preoperative electrocardiogram. At that time, the only statement that could be made was that a positive relationship existed between intraoperative hypotension and the *length* of the operation and postoperative myocardial infarction.

The advances made during the past decade, and especially during the past several years, in preparing the patient with myocardial ischemia for cardiac and other surgical operations have been extraordinary. Patients who only a few years ago would have been considered inappropriate for either a cardiac or noncardiac surgical procedure can now undergo operation with considerable confidence that the myocardium can be adequately protected and arrhythmias and significant complications controlled. Recent studies have indicated an impressive increase in long-term survival in patients with left ventricular dysfunction (ejection fraction less than 40 per cent), following coronary artery bypass grafts (CABG), with an overall surgical survival at 3 years of 86 per cent compared with a medical survival of 68 per cent. Moreover, long-term surgical survival appeared greatest in patients with the *most* severe left ventricular dysfunction, *most* extensive coronary artery disease, and *most* severe anginal symptoms. These data conclusively demonstrate that judicious preoperative preparation, optimal administration of anesthesia, and careful postoperative monitoring have made even the most severely ill patients candidates for extensive surgical procedures.

In this issue, the basic physiologic and biochemical features underlying a variety of cardiac events are forthrightly addressed including concise descriptions of the various pathophysiologic mechanisms of acute ischemia and infarction as well as the role of experimental models in providing objective data for interpretation of these events. Perioperative myocardial ischemia in all surgical procedures can now be assessed on a moment-to-moment basis with accurate detection of the presence and extent of myocardial ischemia. Detection of ischemia as evidenced by ventricular dysfunction as recorded by intraoperative echocardiography has also been a valuable means of continuous surveillance.

The strides made in myocardial protection, especially in the potassium arrested and hypothermic heart, have been of inestimatable value in improving the results of cardiac operations requiring a motionless heart. Of great significance has been protection afforded by selection of the most appropriate anesthetic drugs and continuous changes in their quantity and type reflecting the needs as determined by moment-to-moment monitoring. Finally, cardiologic methods of revascularizing zones of acute myocardial infarction by a combination of balloon dilatation and the use of enzymatic dissolution of thrombi have been clearly established.

In summary, this outstanding review is of maximal current interest, and the group of contributors whom the scholarly editor has assembled have brought the reader a complete state-of-the-art analysis with clear recommendations concerning the prevention of myocardial ischemia. Application of these principles, which are specifically presented in an objective manner, will undoubtedly lead to improved results. The primary role of vigilance in following these patients on an objective basis has been appropriately emphasized together with the bountiful rewards that will surely follow. Having had the unmatched privilege of working closely with Dr. Reves, his characteristic features can be succinctly stated as one who emphasizes excellence in clinical anesthesiology and its interrelationship with clinical investigation and laboratory research. These are remarkably underscored in this issue as the reader will rapidly perceive. It is confidently predicted that this text will have a distinctive impact on the field and will be responsible for a reduction in morbidity and mortality due to myocardial ischemia and perioperative infarction.

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Mechanisms of Myocardial Ischemia and Infarction

Paul R. Wolff, MD, and Michael Nugent, MD†*

Ischemic heart disease remains a major cause of mortality in the United States, accounting for up to 700,000 deaths annually. Since the time that Heberden first described exertional angina pectoris in 1772,[40] a considerable amount of information has been accumulated that has expanded our understanding and guided our treatment of both acute myocardial ischemia and infarction. The concepts of myocardial oxygen supply and demand, atherosclerotic coronary artery stenosis, coronary vasospasm, reperfusion injury, and the role of platelets and prostaglandins represent a sampling of possible mechanisms underlying acute myocardial ischemia and infarction that will be explored in this article.

MYOCARDIAL OXYGEN SUPPLY AND DEMAND

The normal human heart removes about 65 per cent of the oxygen presented to it at rest.[45] As the amount of oxygen required for normal functioning increases, with for example severe exercise, the heart is only able to increase its oxygen extraction to about 80 per cent. Because the heart cannot profoundly increase the amount of oxygen extraction, increasing oxygen demands must be met by an increase in supply. Unlike oxygen extraction, which can only increase about 20 per cent above resting levels, it has been shown that blood flow may increase as much as 500 to 600 per cent with severe exercise.[54]

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A number of factors have been found that have significant effects on the balance between oxygen supply and demand, and they are depicted in Table 1.

Myocardial Oxygen Demand: Major Determinants

Of the numerous factors that have been found to affect myocardial oxygen demand, only heart rate, contractility, and wall tension (preload, afterload) play a major role. An increase in any one of these will result in an increase in oxygen demand.

Myocardial Oxygen Supply

As seen in Table 1, those factors that influence myocardial oxygen supply can be viewed as falling into two distinct categories. The supply of oxygen to the myocardium can be affected by the amount of oxygen in the blood available for release to the tissues as well as by factors that modulate blood flow.

Myocardial Oxygen Supply: Autoregulation

Any increases in myocardial oxygen demand result in increased coronary artery blood flow as a result of coronary arteriolar dilation.[71] Both autoregulation and metabolic regulation of coronary vascular tone are important in maintaining an adequate blood flow to the myocardium during periods of increased demands. Autoregulation, which is believed to be intact between mean arterial pressures of 50 to 150 mm Hg, implies that the coronary vasculature has an intrinsic capability to alter its resistance such that coronary flow will be held constant at a given level of oxygen demand regardless of the arterial perfusion pressure. As a result, under normal conditions aortic diastolic pressure does not play a significant role in determin-

Table 1. *Determinants of Myocardial Oxygen Supply and Demand*

MYOCARDIAL OXYGEN SUPPLY	MYOCARDIAL OXYGEN DEMAND
Oxygen carrying capacity of blood	Major determinants
Hemoglobin content	Heart rate
Hemoglobin saturation	Contractility
Shape and position of the oxyhemoglobin dissociation curve	Wall tension
	Preload
	Afterload
Coronary blood flow	Minor determinants
Aortic diastolic pressure	Activation energy
Autoregulation	Basal oxygen requirements
Intramyocardial pressure	External work (shortening × load)
Heart rate	
Coronary artery narrowing	
Collateral circulation	
Blood viscosity	

ing coronary blood flow. However, under certain pathophysiologic conditions, such as atherosclerotic coronary artery disease or hypotension with the aortic perfusion pressure below 60 mm Hg, this may not be true and a reduced aortic diastolic pressure may severely limit coronary perfusion and blood flow. Other regulators that have been implicated as dilators of coronary resistance vessels in the presence of increased myocardial oxygen demand include hypoxia, acidosis, kinins, adenosine, prostaglandins, and potassium. Some anesthetic agents have been reported to be dilators of the coronary resistance vessels while others have not. Sill et al,[75] using a canine model, found that isoflurane produced dose-dependent arteriolar dilation but did not affect epicardial coronary artery tone. On the other hand, Wilkowski et al,[82] also using a canine model, showed that 60 per cent nitrous oxide did not affect coronary arteriolar tone while it did cause constriction of the epicardial coronary arteries.

Myocardial Oxygen Supply: Intramyocardial Pressure

As the heart contracts during ventricular systole, the intramyocardial pressure rises above that in the coronary vasculature such that effective coronary blood flow to the left ventricle stops. The generation of this intramyocardial pressure tends to be highest in the subendocardium and decreases toward the subepicardium. As a result, the decrease in coronary blood flow is most pronounced in the subendocardium, making this area extremely vulnerable to the development of myocardial ischemia and infarction.[77] Under normal resting conditions, 90 per cent of the coronary blood flow to the left ventricle occurs during diastole.[71] In the presence of ischemia, impaired left ventricular relaxation or systolic function can raise the left ventricular end diastolic pressure (LVEDP). By elevating LVEDP, ischemia can raise the intramyocardial pressure during diastole with the resultant effect of reduced coronary perfusion.

Myocardial Oxygen Supply: Heart Rate

One of the effects of tachycardia in the normal heart is to shorten diastole more than systole. Because the majority of left ventricular blood flow (90 per cent) occurs during diastole, any factor, such as tachycardia, which shortens the interval of time that effective coronary blood flow can occur, is potentially detrimental in a time of increased demand. If the demand for oxygen exceeds the supply, myocardial ischemia and/or infarction are possible.

Myocardial Oxygen Supply: Coronary Artery Narrowing

Any narrowing of the coronary arteries that limits their ability to increase flow during times of increased demand are also potential causes of myocardial ischemia and infarction. Possible etiologies include atherosclerosis, vasospasm, and thrombus formation. These will be discussed in further detail later in this article.

Myocardial Oxygen Supply: Collateral Circulation

Under normal situations, the collateral coronary vessels remain small and essentially nonfunctional. However, in the setting of an atherosclerotic coronary artery stenosis, these vessels, which bridge one major coronary arterial tree to another, may dilate to the point of providing normal resting coronary blood flow to the area distal to the stenosis of a totally occluded coronary artery.[74] Some collaterals become sufficiently large to be able to supply an adequate coronary blood flow, even in the setting of increased oxygen demands. The large nonstenotic coronary artery that gives rise to a collateral must supply not only its own native distal circulation but also that of the diseased vessel via its collateral. Should the pressure and/or resistance to flow fall in its own native distal circulation in response to an increase in demand or by a medication that dilates intramyocardial resistance vessels, a potential arises for coronary steal from the collateral.[11,68] This may represent a possible mechanism of myocardial ischemia and infarction in a diseased coronary artery segment despite the presence of a collateral circulation.

Myocardial Oxygen Supply: Blood Oxygen Carrying Capacity

When the amount of oxygen transported per unit of blood is reduced by anemia, hypoxemia, or an abnormal hemoglobin, the coronary flow must increase to provide oxygen in an amount equivalent to the metabolic needs of the myocardium as compared with situations where the hemoglobin level, oxygen saturation, or hemoglobin structure are normal. This observed increase in coronary blood flow results primarily from metabolic regulation that dilates the coronary arterioles, allowing more oxygen transport to the cells.[25,46] As the intramyocardial resistance vessels dilate, their reserve capacity to dilate in the future with further increased demands is reduced. Under the right conditions of reduced oxygen content of the blood, limited coronary vasodilatory reserve, and increased oxygen demand, the situation could develop where the myocardial oxygen demand exceeds the ability of the blood supply to provide the amount of oxygen necessary for normal functions with the result being myocardial ischemia and perhaps infarction. In contrast, as the hematocrit increases, as in patients with polycythemia, regulatory mechanisms will reduce coronary flow, since the larger amount of oxygen transported per unit of blood meets myocardial oxygen demands.

REGIONAL MYOCARDIAL BLOOD FLOW

Reductions in regional myocardial perfusion resulting in ischemia can occur spontaneously or as a result of a variety of stimuli, including exercise, cold exposure, mental arithmetic, pacing, or smoking.[15,31] The region of the left ventricle at greatest risk for developing reduced blood flow and ischemia is the subendocardium. The subendocardium can be thought of as that area of the heart muscle nearest to the ventricular cavity and thus at the end distribution of the coronary arterial tree. The vulnerability of the subendocardium has been verified by morphologic examinations of the pattern of myocardial infarction that has demonstrated that the areas of ischemic damage are either entirely subendocardial or, in the case of transmural infarcts, are maximal in the subendocardium with reduced areas of damage toward the subepicardium.[29]

The primary mechanism believed to make the subendocardium so vulnerable to ischemia has already been alluded to in the discussion of myocardial oxygen supply. During systole, the rise in intramyocardial pressure is highest in the subendocardium with incremental decreases observed toward the subepicardium, where the intramyocardial pressure is the lowest. As the systolic intramyocardial pressure rises, a point will be reached at which it exceeds the pressure in the coronary arterial tree causing these blood vessels to finally collapse and flow to cease. It is these vessels supplying the subendocardial tissue that will be the first to have their blood flow compromised. The effect of intramyocardial pressure development on coronary blood flow is reflected in the finding that only 15 to 25 per cent of the normal left coronary flow enters that system during systole in humans.[45,85] Only during diastole, when the intramyocardial pressure falls below that in the arterial tree, does the stored blood in the extramural vessels, supplemented by blood from the aorta, perfuse the myocardium. Initially, blood flow during diastole will be directed to those areas of the myocardium with the lowest vascular resistance, which are typically in the superficial areas of the muscle. Blood flow to the subendocardium, which represents the distal portion of the arterial tree and where vascular resistance is higher, will only occur later. Despite these limitations, it has been found that blood flow per gram of tissue in conscious dogs is usually 20 to 40 per cent higher in the subendocardium. In addition, it has been found that oxygen consumption per unit mass in the subendocardium is about 20 per cent higher than that seen in the subepicardium.[45] Experimental work indicates that the coronary arteries are capable of vasoconstriction via α_1- and α_2-adrenergic receptors.[27] While resting vasoconstrictor tone is low, sympathetic activation from baroreceptor reflexes, exercise, and emotion promote α-adrenergic-mediated vasoconstriction, helping to maintain blood flow to the subendocardium. Because the subendocardium is inherently vulnerable, any of a variable number of combinations of factors that adversely affect myocardial oxygen supply and demand can result in ischemia, and perhaps infarction. For example, in the presence of a stenosed epicardial coronary artery, the perfusion pressure distal to the obstruction is lowered. This reduced distal perfusion pressure will have the tendency to reduce blood flow, as expressed in the following relationship:

$$\text{flow} = \text{pressure/resistance}$$

If the flow is inadequate to meet local oxygen demands, regulatory metabolites will be released that can cause further arteriolar vasodilation reducing the vascular resistance and thereby improving flow. A point can eventually be reached where the ability of the arterial tree distal to a stenosis to dilate is exhausted and its ability to increase flow limited. With the coronary vessels near maximally dilated, the existence of a reduced poststenotic pressure and autoregulation exhausted, flow will be compromised most in the area of the subendocardium[45] because the vessels here are subject to the greatest intramyocardial compressive forces.

Any increase in oxygen demand at this time can easily exceed the arterial tree's ability to further compensate and increase flow to match the demand. Decreased subendocardial flow has been demonstrated in dogs with coronary stenosis who were either atrially paced[59] or exercised.[7] When the duration of diastole or the diastolic perfusion pressure is decreased, the subendocardium will receive the least flow. Should ischemia develop with elevation of the LVEDP, the increased intramyocardial pressure present during diastole will act as a further barrier to providing an adequate blood flow to the subendocardium, and a vicious cycle can develop.

ATHEROSCLEROTIC CORONARY ARTERY STENOSIS

Classical or stable angina was described by Heberden in 1772.[40] The classical syndrome of exertional chest pain relieved by rest and nitroglycerin has been ascribed to episodes of increased myocardial oxygen demand that cannot be compensated for by increased coronary flow because of an atherosclerotic coronary arterial obstruction. The vast majority of patients presenting with clinical signs of ischemic heart disease have significant atherosclerotic narrowing of at least one epicardial coronary artery.[38]

Several theories have been proposed to explain the generation of atherosclerotic lesions. The "imbibition" theory suggests that lipids present in blood cross into the arterial wall where they form complexes with acid mucopolysaccharides. An accumulation of these complexes that occur over time form an atherosclerotic narrowing, owing to a deficiency in the mechanism for lipid removal. In the "incrustation" theory, fibrin deposition with subsequent arterial thickening due to the organization of fibroblasts and blood lipids leads to the arterial stenosis. Hemodynamic stress has also been implicated as a factor that can initiate endothelial injury.[67] The role of platelets as a cause of endothelial injury is derived from observations that a number of platelet products can cause vascular damage. The finding that pigs with Von Willebrand's disease do not develop atherosclerosis supports this contention. Adenosine diphosphate (ADP), serotonin, beta thromboglutinin, thromboxane A_2 (TXA_2), histamine, and platelet factor 4 have all been implicated in provoking vascular damage.[34,51,76] In addition, a number of factors have been associated with an increased incidence of coronary atherosclerosis. These include hypertension, hyperlipidemia, smoking, diabetes mellitus, physical inactivity, obesity, emotional stress, and a strong family history of premature atherosclerosis.

The following formula represents an expression that can be used to explain the hemodynamic behavior of a typical high-grade human coronary stenosis.[10,56]

$$P_s = \frac{1.8\ Q_s}{d^4_{min}} + \frac{6.1\ Q_s^2}{d^4_{min}}$$

P_s (mm Hg) is the drop in stenosis pressure; Q_s (ml per second) is stenosis flow; d_{min} (mm) is minimal lumen diameter; 1.8 is the constant accounting for frictional losses caused by blood viscosity; 6.1 is the constant accounting for a transfer of energy. Initially, from the pressure energy of normal arterial flow to the kinetic energy of high-velocity stenosis flow. Second to the turbulent energy of distal flow currents.

The first term, which represents viscous losses, is dependent on blood viscosity, stenosis length, and the minimal cross-sectional area of the stenosis. Except in the presence of a very long stenotic lesion, this first term has little impact on the pressure loss induced by a stenosis. The second term, which represents turbulent losses, is physiologically much more important in determining the drop in pressure across an atherosclerotic obstruction. The relationship between pressure loss and flow is not linear. As blood flow increases, the drop in pressure across a stenosis varies with the square of the flow rate. When flow is normal (1.1 ml per second in the left anterior descending coronary artery) over 75 per cent of the pressure loss across a stenosis is due to this turbulent flow phenomena.[10] In situations such as exercise, anemia, or pharmacologic vasodilation where the compensatory response is that of increased blood flow, the result will be one of reduced pressure across the stenosis, since pressure drops with the square of the flow rate. In a stenosis, pressure loss is also proportional to the inverse fourth power of the minimal lumen diameter. As a result, small reductions in the diameter of the stenosis can be amplified to contribute a large drop in pressure across the stenosis. In a study by McMahon et al of patients with unstable angina who had a minimal stenotic area of 0.63 mm^2, a reduction in diameter of as little as 0.1 mm, due to perhaps vasospasm, thrombus, or passive relaxation of the coronary vessel wall secondary to a drop in arterial pressure, resulted in a significant pressure loss across the lesion and the development of myocardial ischemia.[56,72]

Of the numerous geometric and rheologic variables that have been found to affect blood flow through a stenotic lesion, the most important is the ratio of the minimal cross-sectional area of the stenosis to the unobstructed luminal area.[39] Lesion length, collateral blood flow, and eccentricity are much less important.[15]

When a coronary stenosis occupies less than 50 to 60 per cent of the luminal diameter, the effect on the coronary hemodynamics are negligible. With this degree of stenosis, blood flow is typically able to increase to meet oxygen demands. As the degree of stenosis increases from 60 to about 80 per cent, resting flow to the distal myocardium is maintained by progressive regulatory vasodilation.[60] As previously mentioned, the coronary arterial pressure drops across a stenotic lesion and by compensatory vasodilation the resistance to flow can be further reduced. Thus, blood flow is maintained by arteriolar dilation in the face of increasing stenosis severity until the vasodilatory reserve is exhausted or the stenosis reaches a critical degree of obstruction. At this point, any further increase in demand cannot be matched by increased flow and ischemia will develop. The pressure drop across stenotic lesions in the left anterior descending coronary artery has been predicted for differing degrees of obstruction at a normal steady state of flow (1.1 ml per second).[10] A 60 per cent obstruction will result in a minimal distal coronary pressure of 5 mm Hg less than aortic, while at 70 per cent the minimal distal pressure decreases by 14 mm Hg, and at 80 per cent decreases to 72 mm Hg less than aortic.

CRITICAL STENOSIS

A critical stenosis can be defined as that degree of stenosis for which any further small reduction in the luminal area will cause a significantly reduced blood flow distally. Brown et al, using equations expressing fluid dynamics, predicted that for a typical proximal coronary artery 3 mm in diameter, flow-limiting stenotic lesions would have luminal diameters in the range of 0.5 to 1.0 mm.[10]

Studies in canine preparations have reported that a reduction in luminal area of 80 to 95 per cent represents the degree of obstruction consistent with critical stenosis.[36] Any further reduction in luminal diameter with this degree of obstruction, even as small as 0.1 mm, can markedly increase the resistance to flow and jeopardize distal perfusion.[56] Nichols et al studied patients with proximal lesions of the left anterior descending coronary artery and found substantially reduced myocardial blood flow distal to the lesion when the mean diameter was less than 1 mm, cross-sectional area was less than 0.8 mm^2, and the per cent reduction in luminal diameter exceeded 85 per cent.[60] These findings are consistent with those predicted by Brown et al and for animal preparations with regards to luminal dimensions in flow-limiting critical stenosis.

MORPHOLOGIC CHARACTERISTICS OF ATHEROSCLEROTIC LESIONS

It is true that some atherosclerotic coronary stenoses are unable to change their dimensions. However, it has been found through postmortem examination that a compliant arc of normal-appearing arterial wall borders the lumen in the majority of coronary atherosclerotic stenoses.[30] Such an atherosclerotic lesion is depicted in Figure 1.[10] This area of nonatherosclerotic arterial wall has the potential to alter the stenotic lumen diameter in response to changes in intraluminal pressure, endogenous regulatory mechanisms, or the exogenous administration of drugs. As has been pointed out, changes in luminal diameter of as little as 0.1 mm in the presence of a critical stenosis can have profound effects on stenosis resistance and distal coronary arterial blood flow. If the luminal diameter is narrowed, as by smooth muscle contraction due to vasospasm, distal coronary

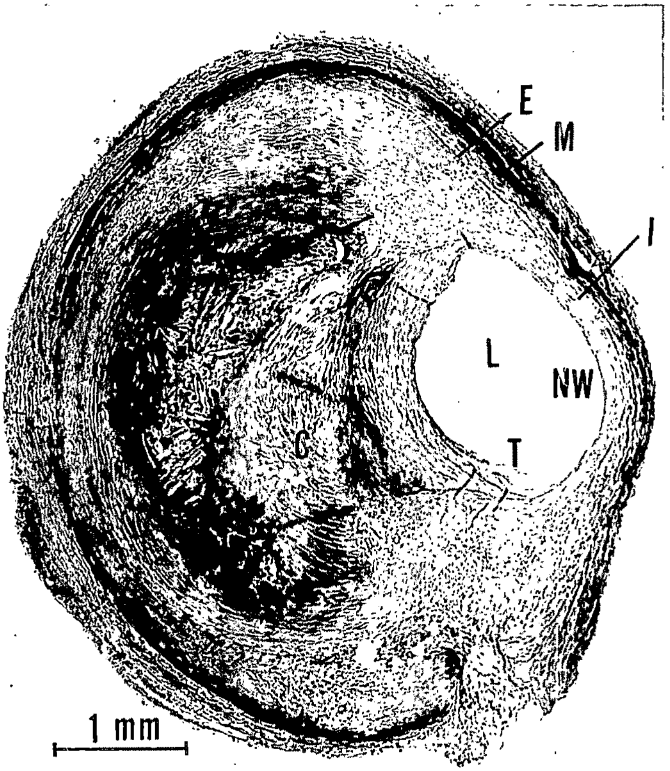

Figure 1. Histologic section cut through a pressure-fixed stenosis of the right coronary artery surgically resected from a patient with variant angina. E = internal elastic lamina; M = arterial media; I = intimal smooth muscle; L = lumen; T = focal mural thrombus; C = collagen (fibrosis) surrounding crystalline cholesterol deposit; NW = the arc of normal wall partly surrounding the remaining lumen. (*From* Brown BG, Bolson EL, Dodge HT: Dynamic mechanisms in human coronary stenosis. Circulation 70:918, 1984; with permission.)

blood flow may be reduced to the extent that ischemia and infarction occur. On the other hand, should the luminal diameter increase secondary to local regulatory mechanisms or the exogenous administration of nitroglycerin, distal myocardial blood flow may increase to the point of restoring a previously jeopardized myocardial oxygen supply and demand situation.

CORONARY VASOSPASM

In 1959, Prinzmetal et al[66] described a clinical syndrome associated with chest pain and ST-segment elevation on the ECG in patients at rest. Since this evidence for myocardial ischemia occurred at rest, unaccompanied by an increase in oxygen demand as is usually seen in patients with stable angina due to atherosclerotic coronary artery disease, a mechanism of reduced blood supply secondary to spasm of the coronary arteries was suggested.[17,35] It was later demonstrated by coronary arteriography that reversible spasm does indeed exist. Coronary arterial spasm has been demonstrated to occur alone or superimposed on existing atherosclerotic lesions. The reduction in blood supply can be so significant as to result in myocardial ischemia, even at rest. While ST-segment elevation on the ECG was initially described reflecting transmural ischemia, ST-segment depression reflecting subendocardial ischemia or no change at all are also possible during episodes of vasospastic angina.

MECHANISMS OF VASOSPASM

The exact mechanism responsible for the development of coronary artery spasm is not known. The role of calcium in the generation of smooth muscle contraction and coronary vasospasm is suggested by the effectiveness of calcium channel blockers in the treatment of vasospastic angina.[17] α-Adrenergic receptor stimulation with resultant coronary artery constriction is believed to be a contributing factor in certain situations such as heavy smoking[86] and mitral valve prolapse.[18] Other possible mechanisms include altered autonomic neural control and the release of local vaosactive mediators. It has been reported that approximately 90 per cent of the patients suffering from coronary vasospasm have significant atherosclerotic coronary artery disease.[2] It has also been found that white blood cells, platelets, and mast cells accumulate at the site of a vascular injury. The release of mediators from these cells such as histamine, leukotrienes, vasopressin, serotonin, prostaglandins, thromboxane, and platelet-aggregating factor could be instrumental in illiciting coronary artery spasm.

UNSTABLE ANGINA

Unstable angina pectorus is defined as angina that has markedly increased in frequency from the previous level of stable angina and/or occurs with significantly reduced effort or at rest. Unstable angina has been associated with a high risk of sudden death, myocardial infarction, and persisting angina pectorus.[19] Mechanisms implicated in the pathogenesis of unstable angina include the accelerated progression of coronary atherosclerosis, coronary vasospasm, intravascular platelet thrombus formation, and plaque fissuring or hemorrhage.

Approximately 90 per cent of patients who develop unstable angina have significant coronary artery disease.[1] Patients with stable, compared with unstable, angina appear to have the same extent and location of coronary artery disease except for a higher incidence of left main disease in patients with unstable angina.[3,4] One other exception is that in patients with unstable angina the stenoses are more often associated with thrombus formation than in patients with stable angina.

The observation that the development of unstable angina is associated with the progression of coronary artery disease is based on cardiac catheterization data. It has been found that approximately 75 per cent of patients previously catheterized during a period of stable angina showed progression of their coronary artery disease when catheterized later after an episode of unstable angina.[3] This is in contrast to patients with stable angina and no progression of their symptoms, who on repeat catheterization had only a 33 per cent incidence of coronary artery disease progression.

It has been observed that about 10 per cent of patients who suffer from unstable angina do not have atherosclerotic coronary artery disease.[1] Coronary vasospasm and thrombus formation offer two possible explanations for the development of myocardial ischemia that occurs in such patients at rest.

There is ample evidence that transient thrombotic obstruction of the coronary arteries is related to unstable angina. Capone et al reported a 52 per cent incidence of coronary thrombus in 44 patients who underwent angiography within 24 hours of the development of rest angina.[16] Similarly, Mandelkorn et al found intracoronary thrombus in four of nine patients with unstable angina at the time of angiography.[53] He found a 70 per cent incidence of intracoronary thrombus in the patients with unstable angina, but none in the patients with stable angina. Platelet attachment to the endothelial surface of an atherosclerotic plaque can reduce blood supply by decreasing the minimal luminal diameter of the stenosis and also by releasing mediators such as TXA_2 and serotonin, which are known to be potent vasoconstrictors. It is possible for a vicious cycle to develop where platelet thrombus formation with subsequent vasospasm leads to further platelet aggregation and spasm until the blood supply is reduced to the point that oxygen demands cannot be met, even at rest. Further support for the role of platelet thrombus formation in unstable angina comes from clinical evidence of a reduced incidence of acute infarction and sudden death in patients treated with drugs such as heparin, streptokinase, and recombinant human tissue type plasminogen activator (tpa), which act to inhibit formation or dissolve platelet thrombus.[9,48,84]

Thus, in unstable angina, it is a reduction in blood supply brought about by a variable combination of progressive atherosclerotic coronary artery disease, vasospasm, and intravascular thrombosis that accounts for the accelerated rate of ischemia and infarction seen in this syndrome.

MIXED ANGINA

Maseri et al introduced the concept of mixed angina, which suggests that some patients can develop angina pectoris as a result of both an increase in myocardial oxygen demand and a transient reduction of coronary blood supply.[54] The syndrome of mixed angina is best exemplified in patients who have a critical coronary stenosis. Any increase in oxygen demand that cannot be met by increased blood flow due to an exhausted compensatory flow reserve will result in ischemia. As has been previously explained, these patients are extremely likely to suffer episodes of reduced blood supply secondary to vasospasm or platelet thrombus formation. Evidence that two pathogenic mechanisms resulting in chest pain with an ECG pattern characteristic of subendocardial ischemia can occur in the same patient has been provided by de Servi et al.[22] They were able to document an episode of coronary vasospasm associated with ST-segment depression in three patients by coronary angiography who developed a spontaneous episode of chest pain. These same three patients had their angiogram repeated when chest pain and ST-segment depression occurred while undergoing an exercise stress test. At this time, no coronary vasospasm could be observed but only the atherosclerotic lesions that were present under the control conditions. It is their belief that the ischemia observed associated with the vasospasm was secondary to a decrease in blood supply at a time of minimal oxygen demand while that observed during exercise was secondary to increased demands not matched by increased blood flow due to the atherosclerotic lesion.

SILENT MYOCARDIAL ISCHEMIA

Chest pain has typically been the marker used to indicate the occurrence of episodes of myocardial ischemia. Substantial evidence has accumulated in recent years to suggest that a significant number of ischemic episodes, and even infarctions, occur in patients who remain asymptomatic.

In patients with typical angina pectoris and proven coronary artery disease by angiography, the appearance of transient ST-segment depression documented by ambulatory ECG monitoring has proven to be a reliable and quantitative marker of episodes of myocardial ischemia. Schang and Pepine,[73] using recorded episodes of ST-segment depression during continuous ambulatory ECG monitoring, have documented that the majority of these ischemic events occurring during normal daily activity are asymptomatic. Erikssen et al documented hemodynamically significant coronary artery disease by angiography in 3.4 per cent of a group of asymptomatic and apparently healthy men.[24] The Framingham study has conducted an extensive 30-year follow-up of patients in a general population and found that upward of 25 per cent of myocardial infarctions may occur unrecognized and that 50 per cent of these may be totally asymptomatic.[15]

The available evidence suggesting that the majority of ischemic events occurring in patients with coronary artery disease is asymptomatic implies that chest pain can no longer be regarded as a reliable indicator of the frequency and severity of ischemic events in these patients.

PLATELETS AND PROSTAGLANDINS

There is substantial evidence that platelets are involved in both the generation and extension of myocardial ischemia and infarction. As previously mentioned, platelets have been implicated in unstable angina,[16,54] acute myocardial infarction, and sudden death. Platelet thrombi may occlude coronary arteries resulting in a reduction in blood supply that cannot meet oxygen demands. Platelet deposition at sites of vascular damage has been demonstrated in animals and humans by use of radioactive indium (III)-labeled platelets.[78] In addition, platelets can significanly reduce myocardial blood supply through release of potent vasoconstrictive substances.

Figure 2 depicts the pathway of conversion for arachidonic acid into biologically active substances. Arachidonic acid is the major precursor of prostaglandins in the body and is found in all mammalian cell membranes. When stimulated, arachidonic acid is transformed by the enzyme cyclo-oxygenase (prostaglandin synthetase) into unstable endoperoxides. In platelets, the enzyme thromboxane synthetase transforms these unstable endoperoxides into the vasoconstricting and platelet-aggregatory substance called thromboxane A_2 (TXA_2). In the vascular endo-

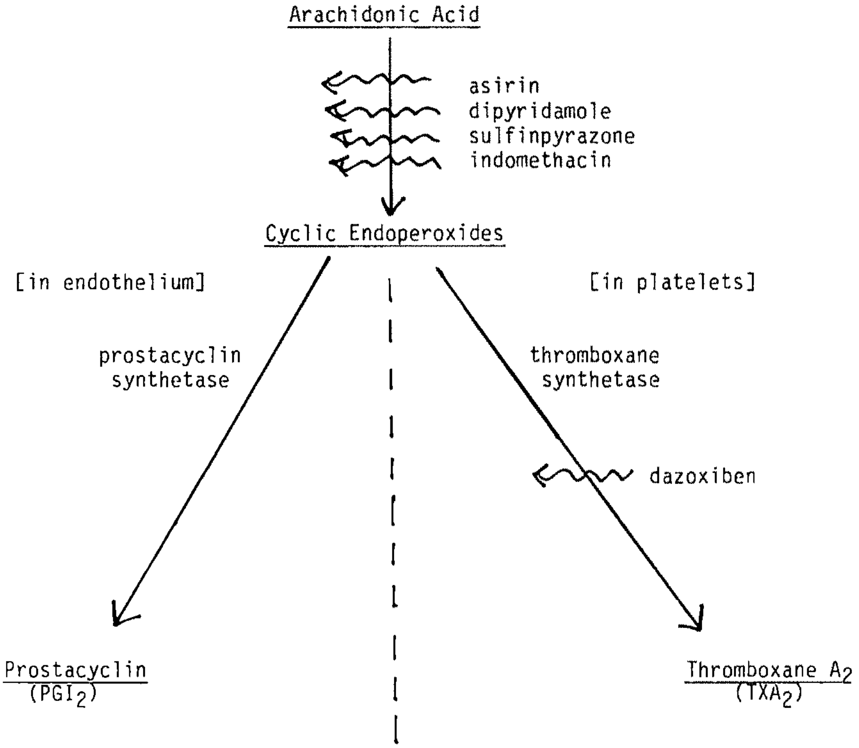

Figure 2. Diagram of the metabolic pathway of arachidonic acid into either prostacyclin or thromboxane A_2. Also shown are sites of inhibition by various drugs.

thelium the unstable endoperoxides are converted by the enzyme prostacyclin synthetase into the vasodilating and platelet-antiaggregating substance called prostacyclin(PGI_2). It is possible that in states of health and contradictory vasoactive and platelet-aggregating properties of TXA_2 and PGI_2 play a role in maintaining normal blood flow by balancing each other's effects. However, evidence exists that this balance is altered in a variety of conditions that could generate or exacerbate myocardial ischemia and infarction.

Increased platelet aggregation with thrombus formation has been demonstrated in patients with coronary artery disease. Turbulent blood flow, ulceration, and hemorrhage in a rapidly developing atherosclerotic lesion may promote platelet adhesion, aggregation, and release of TXA_2 and other vasoactive substances.[83] Platelet thrombus formation has been shown to cause reductions in coronary blood flow significant enough to cause ischemia in animal models of narrowed coronary arteries.[28] It has also been demonstrated that patients with coronary artery disease may generate increased levels of the platelet-derived vasoconstrictor TXA_2, while at the same time producing decreased amounts of the vessel wall-derived vasodilator PGI_2.[58] It has also been observed that the antiaggregatory effects of prostacyclin on platelets is decreased in patients with coronary artery disease.[57] The combination of increased concentrations of the vasoconstrictor TXA_2 at a time when the concentration and effectiveness of the vasodilating and platelet antiaggregatory agent PGI_2 is decreased presents a substantial pathogenic mechanism to the development of ischemia and infarction in a patient with atherosclerotic coronary artery disease.

In addition to unstable angina[57] and myocardial infarction, increased concentrations of platelet-derived TXA_2 have also been documented in association with coronary vasospasm,[62] pacing-induced ischemia,[52] and smoking.[61]

Further support for the role of platelets and prostaglandins in the pathogenesis of myocardial ischemia and infarction comes from studies of drugs that are known to have an inhibitory effect on thrombus formation and prostaglandin production. Antiplatelet drugs such as asprin, indomethacin, and sulfinpyrazone, by inhibiting platelet aggregation, cyclooxygenase, and TXA_2 synthesis, have been shown in clinical studies to reduce the risk of myocardial infarction and death. In two large trials of aspirin in patients with unstable angina, the incidence of acute myocardial infarction and death was reduced from 30 to 51 per cent.[14] Additional support comes from six large, double-blind, randomized trials of aspirin in patients who sustained an acute myocardial infarction. The results of these trials, which showed a reduction in cardiac mortality or nonfatal acute myocardial infarction of 21 to 36 per cent, suggest that aspirin, via its effects on platelet function and thrombus formation, also reduces mortality in this group of patients.

Because aspirin and similar anti-inflammatory drugs block the enzyme cyclo-oxygenase, the production of PGI_2 as well as TXA_2 may be inhibited. By blocking PGI_2 production, the potential for the vasodilating properties of this substance to exert a beneficial effect on coronary blood flow is diminished. As previously mentioned, endothelial damage in areas of atherosclerotic coronary artery stenosis are associated with both a reduced production of and sensitivity to PGI_2. Thus, it may be that aspirin and similar compounds have a predominant effect of reducing the production of TXA_2 in these patients, which could account for part of their beneficial effects in the setting of unstable angina and acute myocardial infarction previously cited. Nonetheless, not all patients with ischemic heart disease show benefit from aspirin therapy. Dazoxiben is a selective thromboxane synthetase inhibitor.[13,20] Since dazoxiben does not block the enzyme cyclo-oxygenase, the production of PGI_2 remains unaffected or even increases at a time when TXA_2 production is decreasing. Thaulow et al reported a significant decrease in the incidence of myocardial ischemia in patients treated with dazoxiben but not with aspirin.[79] It is their belief that the reduced incidence of myocardial ischemia was secondary to improved blood flow to ischemic regions because of enhanced PGI_2 synthesis compared with aspirin.

It has been reported that thromboxane synthetase inhibitors and certain receptor antagonists fail to reverse the cyclic flow reductions seen in canine preparations of a tightly stenosed proximal coronary artery in about 10 to 20 per cent of the cases.[6,12] Ketanserin is a serotonin antagonist that has been found to reverse this cyclic coronary flow reduction when other agents have failed. This suggests that serotonin as well as TXA_2 may be an important vasoactive agent in the pathogenesis of reduced coronary blood flow. Bertha et al[8] found that halothane, but not isoflurane or enflurane, abolished cyclic flow reductions in a mechanically stenosed canine coronary artery preparation. While the exact mechanism for this abolition of cyclic flow reduction is unclear, the difference in chemical structure between halothane (halogenated hydrocarbon) and the other two agents (halogenated ethers) may play a role. In addition, halothane has been shown to be an α-adrenergic blocker and may block the α_2-receptors on platelets.[50] Halothane, in contrast to enflurane or isoflurane, inhibits platelet aggregation in in vitro studies of platelet function.[8] This is depicted in Figures 3 and 4.

DeWood et al reported that 87 per cent of 500 patients with acute myocardial infarction who underwent angiography within 4 hours of the onset of symptoms had total occlusion of the affected coronary artery.[23] Animal studies have suggested that irreversible myocardial cell damage occurs when the time of coronary artery occlusion exceeds anywhere from 20 minutes to 4 hours.[41,47] Based on this information, it would appear beneficial to institute therapy directed at re-establishing coronary blood flow as quickly as possible in the face of acute myocardial infarction. Indeed, the use of thrombolytic agents such as streptokinase and more recently, tissue-type plasminogen activator, have shown that they can produce rapid thrombolysis, reestablish flow, and in some cases, salvage ischemic myocardium.[9,33,84]

REPERFUSION INJURY

Reperfusion of ischemic areas of myocardium shortly after acute coronary occlusion is associated with reduced degrees of

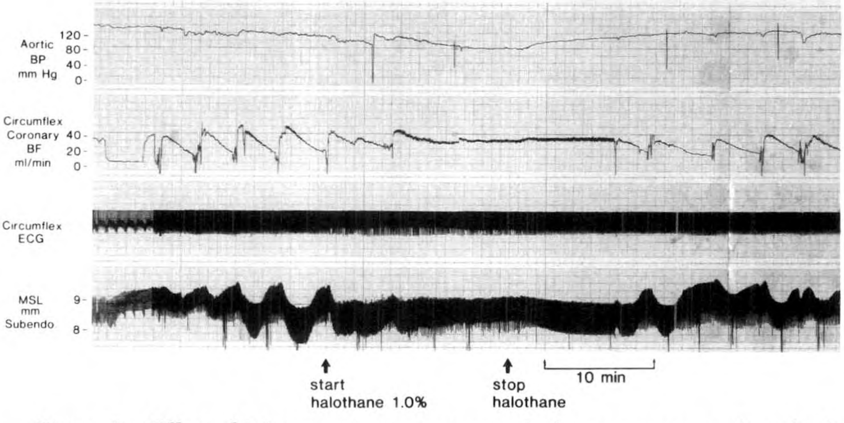

Figure 3. Effect of 1.0 per cent on spontaneously forming coronary thrombi that result in cyclical reductions in coronary blood flow. At the left of the figure during control CFR a 20-second complete coronary occlusion demonstrates absence of significant reactive hyperemic response. This shows that a "critical stenosis" has been produced. Prompt abolition of thrombi formation is seen when 1 per cent halothane is added. The ultrasonic crystal record at the bottom panel shows marked impairment of regional myocardial dynamics during thrombus-induced CFR. With abolition of CFR during halothane ventilation, mild impairment of regional contraction is evident which gradually resolves as halothane is ventilated off. Paper speed 0.10 mm per second. (*From* Bertha BG, Folts JD, Rusy BF: Halothane anesthesia abolishes acute thrombus formation in stenosed dog coronary arteries. 1985 American Society of Anesthesiologists Meeting, San Francisco, CA. Anesthesiology V63(3A):A103, 1985, abstract; with permission.)

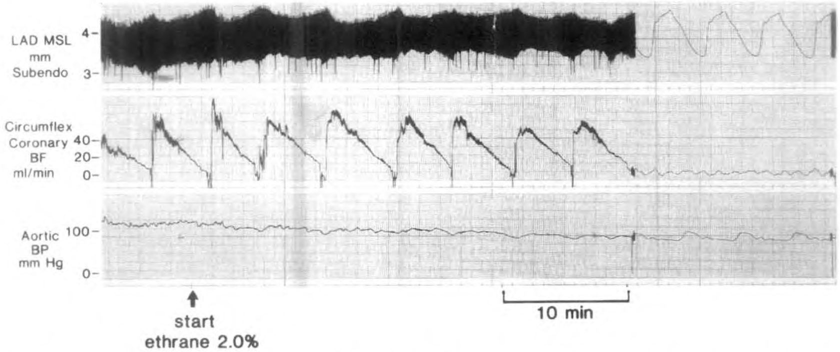

Figure 4. This figure demonstrates the lack of an inhibitory effect of enflurane on the occurrence of coronary thrombus formation/cyclical reduction in coronary blood flow. Isoflurane, in contrast to halothane, also did not inhibit intracoronary thrombus formation. (*From* Bertha BG, Nugent M, Folts JD, et al: Halothane, but not isoflurane or enflurane, abolishes acute thrombus formation in stenosed dog coronaries. American Society for Clinical Pharmacology and Therapeutics, 1987, Vancouver, Canada. Clin Pharmacol Ther 41:181, 1987, abstract; with permission.)

necrosis and death as previously reported. However, evidence is accumulating that reperfusion of ischemic myocardium may also be accompanied by further damage to already jeopardized tissue. Oxygen free radicals, complement, and white blood cells have all been implicated as contributing to reperfusion injury.

Oxygen free radicals are intermediates of oxygen metabolism that contain an unpaired electron and are capable of producing injury by directly attacking unsaturated fatty acids by lipid peroxidation within cell membranes or by initiating a chain reaction leading to generation of other free radicals, such as hydroxyl radicals ($\cdot OH$).[43,55] Peroxidation of membrane lipids by oxygen free radicals has been shown to cause altered mitochondrial function,[37] increased membrane permeability,[44] and decreased calcium transport into the sarcoplasmic reticulum.[42] Mechanisms that have been shown to contribute to oxygen free radical formation include release by neutrophils,[26] prostaglandin synthesis,[49] catecholamine oxidation,[81] and metabolism of xanthine to uric acid by the enzyme xanthine oxidase.[70] Myocardial cells are continually exposed to small quantities of free radicals, especially superoxide anion ($\cdot O_2^-$), but these are typically easily converted to hydrogen peroxide and oxygen by the enzyme superoxide dismutase (SOD), which is found in myocardial cells. Myocardial ischemia has been found to be associated with reduced cellular levels of SOD as well as increased concentrations of free radicals on reperfusion.[21,32,43,55] It may be that the increased free radical generation far exceeds the reduced concentration of SOD during reperfusion of ischemic tissue with the end result being further myocardial injury. Work by Otani et al in pigs has suggested that newborn hearts may be even more susceptible to reoxygenation and reperfusion than older more mature hearts.[63] Newborn hearts were found to have higher CPK release and lower high-energy phosphate stores after reperfusion than hearts 1 week old. This finding may be related to lower protective antioxidative and membrane phospholipid synthetic functions in these animals. The hypothesis that oxygen free radical formation contributes to reperfusion injury is supported by studies that demonstrate reduced infarct size in patients treated with a free radical scavenger, such as SOD, during reperfusion of ischemic myocardium.[5,80]

It has been found that polymorphonuclear leukocytes (PMNs) accumulate at sites of ischemic injury after experimental coronary obstruction in animals.[78] The available data suggests that injury can occur secondary to PMN mediator release either directly or after complement activation.[69] Both the classical and alternative complement pathways have been activated in vitro by cellular fractions of heart muscle.[64] Support for this theory comes from an experimental animal model of coronary occlusion where the complement system was inactivated.[65] Significant reductions in myocardial damage were observed.

SUMMARY

The concepts of myocardial oxygen supply and demand remain the cornerstone by which we can explain the occurrence and guide our therapy for myocardial ischemia and infarction. Atherosclerotic coronary artery disease remains the major etiologic factor in the development of ischemia and infarction. Typically, this results from increased myocardial oxygen demands (increased heart rate, contractility, or wall tension) that cannot be compensated for by increased coronary blood flow due to an atherosclerotic obstruction. While the demand portion of this balance has received much attention in the past, recent findings suggest that the supply side also contributes significantly to the development of myocardial ischemia and infarction. Coronary artery vasospasm and thrombosis are two examples that are receiving considerable investigation. In addition, other new findings such as silent ischemia and reperfusion injury will require us to rethink our clinical management so as to afford our patients the best chance of survival and a productive life.

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Experimental Models of Myocardial Ischemia, Reperfusion, and Coronary Steal: Scientific Foundations and Clinical Significance

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This article explores experimental models of myocardial ischemia and reperfusion and coronary steal versus anesthetics. Is it reasonable to attempt, by any means, to restore perfusion to acutely ischemic myocardium? Are "golden periods" and "border zones" real?

Braunwald editorialized "not since Herrick's original description of acute myocardial infarction (AMI) have so many options been available for the treatment of this condition."[8] Not very many years ago, AMI was "treated" with bed rest, oxygen, attempts at preservation of sufficient cardiac output to preserve vital organ function, and attempts to prevent complications from the bed rest itself. The acceptance of coronary care units implied existence of specific therapy, but they were actually just high-vigilance units, monitoring for arrythmias and low output and attempting to rapidly respond. Today, AMI remains the most common cause of in-hospital death in industrialized nations.

Myocardial infarction (MI) after anesthesia and surgery remains an important issue. Although there is controversy,[44,53] it does not appear likely that we have managed to reduce the incidence or mortality of these perioperative reinfarctions very much, despite greater use of invasive hemodynamic monitoring, beta and calcium blockers, inotropes and vasodilators instead of vasopressors, or use of alpha constrictors plus venodilators to attempt to increase myocardial oxygen supply. No con-

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firmation of the low reinfarction rate in noncardiac injury reported by Rao and El Etr[44] has appeared; indeed, Slogoff and Keats reported that if ischemia was noted during anesthesia and coronary artery bypass graft surgery, infarction occurred with the same frequency, namely about 6 per cent, as that noted nearly always in the past as an overall perioperative MI rate for patients with prior infarcts who undergo anesthesia and noncardiac surgery.[53]

Morbidity of survivors after AMI is another important issue. Degree of left ventricular (LV) dysfunction, determined by size of the original infarct plus any "aftershocks," clearly plays a major role in determining physiologic quality of life afterwards.

During AMI, there are other areas of concern. There must be a time in each patient after onset of symptoms beyond which potential salvage approaches a vanishing point. Although 4 hours is often quoted, this time must vary greatly depending on individual factors including, perhaps, therapeutic ones. For example, if the initial area of ischemia is large, then the resultant demands placed on the remaining functional myocardium will be proportionally great. Border zones surrounding the infarcting area might therefore get less oxygen delivery relative to demand than if the original infarct was smaller, thus the larger the initial infarct, the more likely additional myocardium may be drawn into it. Many other factors, especially collateralization, play roles as well. Therefore, time lines for intervention must be understood and must be achievable in practice on a nationwide basis, not just in sophisticated tertiary care centers, if acute therapy for AMI is to succeed in its twin goals of limiting original infarction and preventing additional tissue death.

Much research in this area has been in animal models, especially the dog. We will try in this article to collate and summarize that research. Our objective is to see if there is a scientific basis for believing ourselves able to prevent mortality, limit infarct size, improve morbidity and additive infarctions, in short, to actually *treat* AMIs. We will also briefly discuss models of production of coronary steal via anesthetics, to see where (or if) this might fit into the picture of perioperative ischemia and infarction.

MYOCARDIAL SALVAGE: POSSIBLE OR NOT?

Occlusion of a major canine coronary artery will cause about 20 per cent of the animals to die within 30 minutes or so.

These are perhaps analogous to humans who succumb during the early period, possibly due to arrythmias, after AMI. If the canine artery is left occluded for 1 to 2 hours, but then released, resultant infarcts, though quite variable in this species, will be smaller than after permanent occlusion. After 4 to 6 hours of occlusion, now releasing the ligature produces both a higher immediate death rate and, often, a larger resultant infarct in the survivors. In this reperfused group, after 4 to 6 hours occlusion, intramyocardial hemorrhage, edema, and other evidence of breakdown of capillary integrity can be noted in the infarcted zone.[32,45]

The issue is much more complex than this. Extent of infarction seems to depend to some extent on method of measurement. With wall motion studies (ventriculography) during AMI, and even for several days after AMI, infarction areas often appear considerably worse than can be later confirmed at histology. This discrepancy led to yet another concept, the "stunned" myocardium, tissue that is dysfunctional during and after AMI but which is somehow eventually salvaged, even to the point of functional return.[14,29,49,56] This helps explain why there are all sorts of discrepancies in the literature as to efficacy of various treatments for AMI. This salvaged myocardium may be able to return to full function, or it may remain somewhat contractile but not able to carry its prior share of the afterload. Ellis et al quantitated the relationship between actual transmural extent of AMI and eventual associated contractility patterns in dogs after LAD coronary artery ligation.[15] They studied permanent occlusions versus occlusions lasting 2 hours. They compared two-dimensional echocardiographic computer-assisted regional wall motion analyses with eventual histologic infarct localization by staining technique. Both of these techniques are widely used. The staining technique involves a compound called triphenyl tetrazolium chloride (TTC). This substance stains tissue red whenever it encounters lactic dehydrogenase enzyme present, that is, it stains previously "living" tissue, though it does not differentiate between that tissue that was alive and that tissue that was alive and contracting well. They compared noninfarcted regions with those containing infarct with respect to wall thickening to measure function.[15] In the noninfarct-containing regions, the wall thickened 59 ± 16 per cent during systole. In infarct-containing regions, in contrast, the wall thickened from −4 to +47 per cent depending on (to a reasonable degree at least) how much histologic infarct was later noted to be present in the region studied.[15] The reason for all this detail about this study is to emphasize the complexity of studies of myocardial salvage. In the study by Ellis et al, there was a good correlation (0.87) between degree of regional function measured by wall thickening, and percentage of that region histologically infarcted.[15]

Most clinical trials that have attempted to measure salvage have *not* reported much if any recovery of overall LV function, as measured by ejection fraction, after reperfusion. Two such studies, the Western Washington Intracoronary Streptokinase Trial[26] and the European Registry[47] found negligible increases in ejection fraction compared with controls during AMI, namely 0 and 5 per cent, respectively, when patients were studied 4 weeks or more after AMI. This result might have reflected that little salvage had occurred, but alternatively it might have reflected that surrounding well-perfused myocardium was simply compensating for the poorly perfused myocardium in the AMI itself. Global ejection fraction is not a sensitive or specific marker of regional dysfunction. Ellis et al suggest that an additional explanation might be that "(resultant) function may not be linearly related to the amount of salvage and that salvage of small amounts of myocardium is of little functional consequence."[15] Indeed, in the Ellis et al canine study, if less than 40 per cent of an expected resultant infarct was salvaged, there was little benefit with respect to subsequent overall myocardial function.[15] Myocardial salvage has recently become of great import in the controversy over whether intravenous or intracoronary streptokinase, or intravenous tissue plasminogen activator (TPA) might actually salvage myocardium that otherwise would be infarcted, despite the obvious fact that both these compounds do dissolve or remove at least some thrombi in infarct-related coronary arteries during AMI. More will be mentioned about this.

The issue of salvage and how to measure its functional consequences is by far the most central issue with respect to development of an experimental model in animals, and with respect to understanding the various human trials of promising agents. Actually, the issue of when to perform intervention, be it medical or surgical, is somewhat less interesting (more academic) since clinically, physicians are likely to try to perform whatever intervention happens to be in vogue or available to them just as soon as practicable after the diagnosis of AMI is entertained.

Hammerman et al, using a canine model, and two-dimensional echo versus eventual histologic outcome, attempted to study resultant mass of necrosis versus prior area "at risk."[21] To study the area at risk, one injects a marker (dye or radioactivity) into the coronary artery just before it is ligated. This presumably then delineates the area that was perfused by that coronary artery just before the ligation. In the study by Hammerman et al, dogs had either 6-hour or 2-hour coronary occlusions; all groups had a 4-hour period of reperfusion.[21] When there was a 6-hour occlusion, the resultant mass of necrosis was 74 per cent of the area at risk. With the 2-hour occlusion, the area of necrosis was only 44 per cent of the area at risk. This is obvious salvage, but despite this, during life, two-dimensional echocardiographic wall motion studies could not detect this large histologic difference. In other words, wall motion abnormalities during AMI, during reperfusion, were of similar extent in both groups.[21] The conclusion of Hammerman et al bears mentioning.[21] The contention is that it might not be prudent to conclude, based on in vivo wall motion studies in humans, that particular interventions were or were not effective.[21] It seems logical that if well-perfused myocardium can compensate during acute myocardial infarction by increasing its contractility to compensate for areas not well enough perfused to contract, but not dying, then overall functional indices, especially ejection fraction, might be maintained fairly well throughout AMI at least in survivors. If so, then myocardium that was eventually salvaged by some intervention or other might go undetected. Thus, it might not be reasonable to conclude, as have several authors[26,44,47] that various interventions do not help to salvage myocardium. Is it worth salvaging these smaller amounts of tissue? Those who state that there is no superfluous myocardium might be reminded of the mortality and morbidity associated with all the interventions reported and proposed to date, most certainly including streptokinase and/or TPA.

Therefore, there are two sides to the salvage question. One side contends that it is possible to salvage smaller masses of myocardial tissue and yet not detect the resultant salvage by global or even regional wall motion analysis. This side would contend that therapy should be pursued with great vigor. The other side contends that if the global function is not likely to be improved by such "small" salvage then maybe it is not worth the chance of morbidity/mortality during and following medical and/or surgical interventions. By "small" salvage, that is, undetectable in vivo, a salvage of less than 40 per cent of an expected infarct is generally what is meant. This may not seem small to some readers. It is hoped that the preceding discussion will give the reader an idea of the complexity of this issue. It is hoped the perusal of recent newspaper accounts of the heated debate at the Food and Drug Administration over whether or not to release TPA to the public (the drug company won, it has now been released) should give us cause to consider the enormous cost to the health care consuming public of such decisions about efficacy. Nonetheless, the release of TPA is currently being hailed as "long overdue" and indeed may be so, though actual functional salvage, minus the morbidity and mortality of the therapy itself, may not be as impressive as hoped.

Nuclear magnetic resonance (NMR) has been used in dogs to study another aspect of reperfusion, namely the formation of edema, by Brown et al.[9] They reported that experimental ischemia of at least 1 hour resulted in myocardial edema detectable by NMR. The disappearance of this edema could be followed with serial NMR studies. Use of edema regression rates as evidence for salvage has not yet "caught on" in human trials of therapy, but is a possible approach.

Computerized tomographic methods have also been used to study the reperfusion versus salvage question. Mancini et al, using dogs, studied permanent versus 2-hour occlusions followed by reperfusion.[31] After several days, both groups experienced severe early changes, but the permanently occluded group remained severely depressed with respect to regional wall thickening 3 days later, whereas the reperfused group, despite equally severe initial wall motion depression, experienced some improvement at 3 days. The wall thickening, as expressed as a per cent of control, in the ischemic zones of the nonreperfused animals was only about 2 per cent at 3 days, whereas wall thickening had improved to about 17 per cent of control at 3 days in the reperfused animals. Although this seemed to be an improvement, these changes were not statistically different. As noted previously, despite not being able to document salvage by reperfusion after 2 hours occlusion using the in vivo techniques, there was clear salvage histologically.[31]

The literature regarding whether or not reperfusion therapies with new drugs, operations, or procedures like angioplasty has resulted in actual salvage must, therefore, depend on how salvage was measured, whether it was determined using indices of global or regional myocardial function, whether or not histologic salvage was also correlated, and whether or not the actual salvage resulted in any worthwhile improvement in subsequent myocardial function. The mortality and/or morbidity that occurred during the "salvage operation" must also be taken into effect.

CORONARY COLLATERALS: DOGS, PIGS, AND HUMANS

The dog has a coronary circulation collateralized anatomically, that is, not in response to disease. It is possible to occlude a major coronary artery and not produce any histologic infarct. Radioactive microspheres, injected into a coronary artery just prior to experimental occlusion, permit subsequent autoradiographic techniques to be used to determine the area at risk. This is the area where the microspheres are lodged, and it is presumed to be the area supplied by that coronary artery just prior to its occlusion. If the animal survives, after a waiting period of 6 hours to 2 days, at autopsy, TTC staining will reveal the actual resultant histologic infarct, which then can be expressed, with its at-risk counterpart, as a per cent of the original area at risk. In dogs, the infarct size taken as a per cent of the original area at risk, is quite variable (ranging from 0 to 75 per cent). This fact alone calls into question canine studies wherein salvage after reperfusion is compared with salvage after permanent ligation.

It has been contended that because the dog is a collateralized animal, it might be suitable as an analog for human disease-related coronary collaterals. On the other hand, the dog's collaterals are not developed in response to disease, although they seem to somehow "pop open" or otherwise appear subsequent to a relatively short circa (1 week) gradually produced occlusion of a major coronary artery, using an ameroid constrictor. Ameroid is a casein-derived substance that, when placed inside a metal ring around an artery, gradually swells againt the ring, occluding the artery over a week or so. Dogs, left to their own devices, generally do not die of coronary artery disease. Humans, especially those who have not had an MI or long years of chronic angina pectoris, do not have well-collateralized myocardium. Therefore, it seems to this author that the dog is at best a problematic model of human disease-related coronary collateral circulation.

The pig, in sharp contrast, is such a "noncollateralized" animal that 75 per cent or more of the area at risk as determined previously, will infarct after a permanent coronary artery occlusion. Further, on TTC staining, pig infarcts appear to be much more homogenous than do those in dogs, and indeed appear very human-like in this regard. With such an end-arterial coronary circulation, studies of reperfusion of temporarily occluded coronary arteries in the pig would be expected to be much different than those cited previously in the dog. If there were few or no collaterals in the pig, then the infarcting area would be expected to suddenly receive much more blood flow during reperfusion than in the dog wherein anatomic collaterals might come into play prior to reperfusion during the occlusion. Because of this, it seems logical, although there is little evidence, that reperfusion might be *more beneficial* with respect to salvage of tissue in the pig than in the dog. If so, then reperfusion might be more beneficial with respect to tissue salvage in humans also for the same reasons. The point of this discussion is not particularly to demand that future animal models for coronary artery research be developed in pigs rather than dogs, but at least to make the point that the value of reperfusion with respect to salvage of myocardium may not be well delineated in dogs with naturally collateralized circulations.

We have precious little knowlege about development of collaterals in response to coronary artery disease. We cannot predict their existence in a given patient, and we do not know how to study their function. Blanke et al chose to replace the term *collaterals* with *residual flow to the infarct zone.*[5] They studied the latter with coronary angiography in 130 patients during AMI. In 36 patients, the artery supplying the AMI was incompletely obstructed, that is, there was residual antegrade flow to the infarct zone. In 56 patients, complete inflow obstruction was observed but there was residual flow, presumably by collaterals into the infarct zone. In the remaining 38 patients with AMI, there was neither antegrade nor collateral flow observed going into the zone of infarction. Despite these great differences in angiographic appearance of the AMI, ejection fractions in these three groups of patients averaged 55, 48, and 50 per cent, respectively. To be sure, the group with remaining antegrade flow had statistically better ejection fractions; these three nearly equal averages are convincing evidence that global indices of function are of little value in assessing eventual salvage, efficacy of therapy, or degree of collateralization, presumably because of the compensation of surrounding viable perfused myocardial tissue. This study also concluded that the patients in whom there was observable collateral flow into the zone of AMI did indeed have longer histories of angina pectoris.[5]

In the study by Blanke et al, 37 of the 130 patients did not undergo any reperfusion therapy, but did have repeat angiography at a later time.[5] Ejection fractions did not change between the acute and chronic stages of infarction, either up or down, if there was, previously, observable antegrade flow during the AMI. Patients who had observable collateral flow into the AMI zone also did not deteriorate later with respect to their ejection fractions. In sharp contrast, the patients who had no observable antegrade or collateral flow into the AMI zone, who survived, did undergo significant worsening of ejection fraction later in time (average decrease 10 per cent). This is excellent evidence, in humans, that presence of collateral flow into an AMI is a very important determinant of extent of functional salvage, on the one hand, and probably of whether any reperfusion intervention will have demonstrable efficacy, on the other hand.[9] It is logical that the patient having an early MI, who has not had prior MIs, who has had a long or any history of angina, might not be expected to have much collateral or "residual" flow into the AMI zone. These patients might be expected to benefit most from reperfusion undertaken at the earliest possible moment. On the other hand, it is obvious, at least logically, that these patients would be just the ones in whom the "golden period" for reperfusion would be the shortest of all. In other words, these are the patients who would need to be treated earliest if significant myocardial salvage was to take place. Unfortunately, it is just such patients in whom denial of the developing AMI might be expected to occur, if for no other reason than the patients are likely to be less familiar with this kind of pain. This denial might then be expected to delay therapy the longest, since these patients would be least likely to understand what was occurring. The author hopes that this discussion also serves to highlight the complexities associated with the simple starting idea of attempting reperfusion during AMI by whatever means. The subject is not simple. Although this discussion used as an example the elegant studies of Blanke et al,[5] there are numerous other studies[16,27,34,39,48,50] that are in substantial agreement with these findings and speculations.

OTHER FACTORS AFFECTING OUTCOME-ADVISABILITY OF REPERFUSION DURING ACUTE MYOCARDIAL INFARCTION

Sheehan et al studied 47 patients with AMI who underwent reperfusion that was proven angiographically to have occurred ater streptokinase therapy given directly into the coronary artery.[51] Although their end point was recovery of LV function after perfusion, they avoided the global compensation problems mentioned previously by measuring regional LV function via ventriculography and dividing the heart into numerous separate regions for quantification. They found that an important determinant of eventual functional improvement was the diameter of the residual stenosis after reperfusion was achieved. For some reason, relatively little attention has been paid to this concept. Lysis, somehow, of the thrombotic "straw that broke the camel's back" still leaves the patient with a residual coronary atherosclerotic plaque producing a stenosis. Sheehan et al clearly showed that LV functional outcome did not dramatically improve after AMI if this critical stenosis was allowed to remain.[51] This means that mere achievement of angiographic evidence that some blood flow has been restored past a previously completely obstructed area is probably not enough to assure adequate flow. Sheehan et al also reported that patients in whom angiographic reperfusion was achieved within 2 hours of onset of symptoms had better resultant regional function than those in whom reperfusion was not achieved until greater than 2 hours had elapsed.[51] This idea that adequate flow, not just angiographic evidence of some reperfusion, is essential was also reported by Marx et al.[33] Harrison et al added to this knowledge by reporting that there was a considerably greater risk of rethrombosis and therefore, further or continued AMI when the residual stenosis associated with the thrombus was severe.[22] It should be added that there is not complete agreement on this point. Smalling et al could not correlate functional outcome with angiographic estimate of residual stenosis.[54] Despite this, as Sheehan et al pointed out, thinking of residual stenosis in terms of percentage occlusion may be insufficient because the actual shape of the cross section at the stenosis may not give an accurate estimate of what is really occurring.[51] Also, there may be disease at that point not revealed by angiography that has caused an acute thrombus to form in that location in the first place.

In the series of Blanke et al, about a third of the patients had observable collaterals.[5] On the other hand, Sheehan et al reported that only three, that is, 6 per cent of their patients had collaterals.[51] Despite this, Sheehan et al reported better functional results.[51] Perhaps presence of collaterals indicates greater overall severity of disease at the small vessel level.

Mathey et al considered that if reperfusion could be achieved within 2 hours of onset of symptoms, wall motion was near normal in 82 per cent of the patients who had chronic follow-up.[35] On the other hand, if reperfusion occurred 2 to 5 hours after symptom onset, wall motion was eventually improved toward normal in only 46 per cent of the patients. This study also indicates the difficult logistical problems involved, because only 17 of the 69 patients, for whatever reason, had reperfusion established within 2 hours of onset of symptoms. Braunwald has noted that it is unlikely that a very large percentage of Americans undergoing AMI could be treated within 2 hours of onset of symptoms with any remotely complex form of therapy.[8] This is why cardiologists have been discouraged at thinking about the necessity for doing angiography, balloon angioplasty, intracoronary injection of drugs, etc., as "therapy" for AMI. The logistical problem of transporting patients within 2 hours of onset of symptoms, to a facility where such complex therapy could be performed on a 24-hour per day basis, with a reasonably low morbidity and mortality from the treatment itself, is a depressing specter.

Another aspect of the reperfusion question was studied by Wei et al.[57] They studied untoward reflexes and arrythmias that might be stimulated by achievement of reperfusion in a group of 41 patients with AMI. Of these, 27 had "successful" reperfusions, yet in this successful group, 17 developed major bradycardia with hypotension and another patient developed tachycardia with hypotension, all at the approximate time of achievement of recanalization of the vessel by whatever means. It appears from this study[57] and other evidence that successful reperfusion may stimulate some untoward reflexes such as the cardioinhibitory vasodepressor (Bezold-Jarish) reflexes. It has been speculated[40,57] that occurrence of this vasodepressor reflex might even be used to *predict* spontaneous occurrence of reperfusion, the incidence of which is entirely unknown. All of this does bring up yet another aspect of the discussion of how success in any kind of AMI "treatment" might be evaluated. Ejection fraction is known to be a markedly rate-dependent measure. If "control" versus "post reperfusion" versus "chronic" ejection fraction studies are not performed at similar heart rates, and it is very unlikely that they could be, then results based only on global indices such as ejection fraction, are clearly questionable. Clearly reflex vasodilation and bradycardia are well known to be associated with coronary angiography.[13,43,58]

Ganz reported that reperfusion was accompanied by arrythmias in many patients, and that some of these were life threatening.[17] It is, therefore, entirely possible that some patients, maybe a significant number, would be lost during the achievement of reperfusion! Clearly, careful readiness must exist for the treatment of these arrythmias, which can never be considered benign. So if there are going to be patients lost during reperfusion, due to arrythmias or whatever else, then this "price" must be quantitated against purported salvage benefits from any particular kind of reperfusion therapy. Again, it is to be emphasized that the "treatment" of AMI is not just a simple matter of opening up the occluded artery as soon as possible after onset of symptoms.

DIFFERENCES IN METHODOLOGY VERSUS OUTCOME

Details of these new forms of therapy are beyond the scope of this article and are discussed in the article by Hinohara et al in this issue. Suffice it to say here that streptokinase,[20,28,48] given via the coronary or intravenous route, urokinase,[36] intracoronary beta-adrenergic blockade,[19] acutely performed balloon coronary angioplasty,[23,25,42] acutely performed coronary bypass,[12,30,52] coronary bypass performed after streptokinase therapy, digitalis plus 1 or more of the above,[3] converting enzyme inhibitors,[24] new beta-adrenergic blocking agents like exaprolol,[41] the alpha-adrenergic antagonist nicergaline,[7] treatment of arrythmias with naloxone during reperfusion,[2] various anti-inflammatory drugs,[38] and most recently tissue plasminogen activator,[11] have all been reported to be successful in varying degrees with respect to myocardial salvage during AMI. It is valid to state that there is no "treatment of choice" for AMI yet, nor is there a sequence of treatment of choice established. One of the purposes of this article is to make the reader aware of the fact that we are still not clear at all as to how to actually determine salvage and/or the functional result of same. If we cannot understand how to measure either salvage or its functional result, then it is very likely that there will be continuing controversy over efficacy of various proposed and attempted therapies. Lest this prediction look too gloomy, it is important to point out that today there are, indeed, major efforts defining the role of new therapy. AMI is no longer a disease treated with bed rest and "watchful waiting."

MODELS OF CORONARY STEAL VERSUS ANESTHETICS

In 1983, Reiz et al studied 21 patients given a protocol isoflurane anesthetic wherein mean arterial pressures averaging 113 mm Hg in the awake unpremedicated state, were rapidly dropped to a group average of 68 mm Hg with isoflurane anesthesia.[46] This resulted in significant tachycardia. Ten of the 21 patients developed signs of myocardial ischemia. Because coronary blood flows were relatively well maintained compared with levels expected with the degree of myocardial depression observed, the authors contended that isoflurane was a direct, that is, pharmacologic, coronary vasodilator and that the ischemia observed probably was caused by a mechanism involving coronary steal.[46] Other studies in humans by Moffitt et al also have been interpreted to mean that isoflurane is a direct coronary vasodilator capable of causing coronary steal.[37] The problem with this human model is that changes in peripheral vascular resistance, and isoflurane is certainly a peripheral vasodilator, are of themselves, important reflex coronary vasodilating stimuli. A direct pharmacologic dilation mechanism by isoflurane does not need to be invoked to account for the observed relative maintenance of coronary blood flow above that expected by either measured or predicted demand. If indeed this preservation of coronary blood flow is more on a reflex basis than on a direct pharmacologic basis, then clinically relevant steal with this anesthetic would be less likely to be involved. Indeed, also in humans, Tarnow et al paced patients with coronary artery disease in the awake state until angina occurred.[55] The heart rates at which this angina occurred, plus electrocardiograms, were recorded at that point. Next, they anesthetized the patients with isoflurane and again recorded the heart rates at which an EKG pattern similar to that that occurred during awake angina (obviously asking about angina was impossible) were again recorded. Under isoflurane anesthesia, heart rates could be stimulated to considerably greater levels by electrical pacing before ischemic patterns emerged despite presence of known severe coronary artery disease. This was interpreted by Tarnow et al[55] to indicate that isoflurane was actually *protective* against myocardial ischemia, exactly the opposite conclusion arrived by Reiz et al[46] and Moffitt et al.[37] It is known that isoflurane preserves various cardiovascular reflex mechanisms more than relatively equi-anesthetic doses of halothane or enflurane. Thus, the previously mentioned reflex mechanisms might well account for at least some of the results implicating isoflurane via a steal mechanism. This author does not believe that the results of Reiz et al[46] or Moffitt et al[37] are conclusive evidence that a coronary steal mechanism necessarily accounts for the ischemia encountered in these patients.

Buffington et al developed a canine model in which coronary steal was conclusively demonstrated with isoflurane, but unfortunately chose to utilize equi-MAC concentrations of isoflurane versus halothane instead of concentrations that produced equal coronary perfusion pressures.[10] With isoflurane, at the dosage chosen (during "basal" anesthesia with chloralose, another variable in this study) the coronary perfusion was 41 mm Hg, but with halothane in equi-MAC dosage, resultant coronary perfusion pressure was 51 mm Hg at the same coronary flow, a large difference, considering that control, that is, basal chloralose anesthesia perfusion pressure was only 58 mm Hg. These animals had been previously subjected to chronic (1 week) coronary occlusion and production of collateral-dependent myocardial zones. With radioactive microspheres, collateral to normal flow ratios were measured and were found significantly reduced with the isoflurane conditions mentioned previously (only one dose was studied). This is conclusive evidence that coronary steal can be demonstrated with 1 MAC isoflurane, in dogs, with experimentally created collateral dependent zones, at coronary perfusion pressures of 41 mm Hg, but is not a valid dose-response comparison to halothane.

A third model of coronary steal versus anesthetics is a simple sounding one. Bollen et al[6] using pig coronary arteries and Blaise et al[4] using dog coronary arteries, mounted tiny rings of these vessels in specially designed transducer baths. After first constricting these in vitro mounted arteries with potassium or prostaglandin, clinically relevant dosages (in dose-response fashion) of either halothane or isoflurane, were tested for their abilities to dilate these previously constricted arteries. In fact, if anything, halothane proved to be a better dilator than isoflurane! These studies show that neither halothane nor isoflurane are particularly potent or effective direct pharmacologic coronary vasodilators at least at the epicardial level. Further, these studies are evidence that if indeed direct coronary vasodilation is occurring during clinical anesthesia, it is occurring at a much smaller, probably arteriolar, level with these agents.

A fourth model for studying coronary steal versus anesthetics is that of Gilbert et al, which uses coronary reactive hyperemia and measurements of coronary reserve.[18] A 10- or 15-second occlusion of a coronary artery is the most potent stimulus known for distal coronary vasodilation. Release of said occlusion is immediately followed by a marked increase of flow velocity. Gilbert et al reasoned that using incrementally increased levels of either halothane or isoflurane, if either drug was a direct pharmacologic coronary vasodilator, would be associated with decreases in coronary ability to produce reactive hyperemia after a 10- or 15-second occlusion, because the distal vessels should already have been dilated in response to the anesthetic.[18] In other words, coronary reactive hyperemia should be lost if indeed these agents are direct pharmacologic vasodilators. Surprisingly, Gilbert et al found the opposite of that which might be expected from the previous speculations by those who contend that isoflurane can be causative of coronary steal. Gilbert et al found that with isoflurane, given in incremental doses until the death of the animal, there was much better preservation of coronary reactive hyperemia and coronary vascular reserve in response to 10- to 15-second occlusions than was the case with halothane, approximately twice the preservation, in fact.[18] This again is certainly not evidence that isoflurane is a direct pharmacologic vasodilator, and is evidence against the idea that isoflurane would likely be productive of clinically relevant coronary steal. On the other hand, these studies were done in normal pigs without disease-related (or anatomic) collaterals.

Summing up these various "models" for study of coronary steal, it is important to state that isolated research studies in controversial areas such as this particular one should not be taken out of context and should not be immediately translated into clinical decision making with respect to which anesthetic to use for which particular patient without a thorough understanding of the consequences of such decision making. It is invalid, in this author's opinion, to editorialize, as Becker recently did,[1] that isoflurane may be "dangerous" to use for anesthesia in patients with coronary artery disease. Becker stated no opinion and provided no data (for indeed there is none) that would indicate that *some other anesthetic is safer* in these same patients, considering the fact that they do indeed need some sort of anesthesia. Slogoff and Keats reported that if perioperative myocardial ischemia occurred, perioperative MI followed approximately 7 per cent of the time.[53] Their contention was that this is evidence that perioperative ischemia needs careful attention, treatment, etc. No one could dispute this, but one can turn their results around and ask the question "why did the other 93 per cent of the patients *not* develop myocardial infarctions?" The present author believes that there is increasing evidence to indicate that the answer might be that the event that tips the balance toward infarction during or following ischemia might be *thrombosis*. It seems logical and likely to this author that future therapeutic trials aimed at reducing incidence of perioperative MI will be aimed at predicting, preventing, or eliminating thrombosis. Based on the weight of evidence to date, this observer does not believe that any particular anesthetic agent, given in clinically relevant fashion, that is, making every attempt to avoid hypotension, tachycardia decreases in myocardial perfusion pressure and oxygen supply, will prove significantly more "dangerous" than other agents. This observer is not enamored with the clinical relevance for anesthesiologists of the catchy term "coronary steal," and hopes that we will not be distracted from studies aimed at understanding why ischemia sometimes but not usually leads to infarction.

SUMMARY AND CONCLUSION

The occlusion of a coronary artery, acutely, in dog, pig, or man, followed by release after a few seconds or minutes, will not be followed by an infarction. If the occlusion is held for 20 minutes, there will be damage. If the occlusion is maintained for 2 to 6 hours, there will be a point after which release of the ligature will not have measureable benefit. In man, this "golden period" wherein reperfusion, however achieved, is likely to be most beneficial, is probably 2 hours, with perhaps an additional "silver" period (this is my term) of another 2 to 4 hours wherein some functional salvage may be achieved from reperfusion. It is clear that there is a period during which reperfusion will be likely to be associated with some benefit at least during AMI.

How much benefit will occur is dependent on many factors including size of the residual stenosis, presence or absence of collateral inflow to the ischemic zone, whether or not abnormal reflexes and/or arrythmias occur during the intervention itself, and presumably other morbidity associated with or as a result of therapeutic interventions. How much benefit will accrue may also be dependent on how myocardial salvage is measured.

The question of efficacy of reperfusion is extremely complex and must examine in detail the question of salvage because if the end point is to be measureable, functional improvement, then the results achieved with reperfusion, at least on an experimental basis, are not nearly as encouraging as those achieved when the end point is either regional functional improvement or histologic salvage. Despite this, the latter two methods of measurement do make some sense because it is logical that if there is more tissue alive and functioning at least to some extent, that tissue might be eventually likely to participate in better physiologic quality of life, however difficult the latter is to measure.

This observer's answer to the question "Is there a scientific foundation to the concept that reperfusion during AMI is a worthwhile therapeutic goal?" is a heavily qualified "yes," given an understanding of the complexity described previously.

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Perioperative Ischemia and Infarction: Cardiac Surgery

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Reduction of coronary artery diameter by 80 per cent causes distal compensatory vasodilation in an attempt to maintain normal coronary flow. With such a critical stenosis, the capacity for additional dilation or coronary reserve is absent. The pathophysiologic effects of coronary stenosis depend on the balance between myocardial oxygen supply and demand. Factors affecting supply and demand are discussed in the article "Mechanisms of Myocardial Ischemia and Infarction" in this issue.

Myocardial blood flow depends on blood pressure at the coronary ostia (coronary perfusion pressure is the difference between aortic diastolic pressure and ventricular end diastolic pressure), arteriolar tone, collateral development, intramyocardial pressure, and extravascular resistance. Coronary flow occurs principally in diastole because the increased intramyocardial pressure during systole limits coronary flow (systolic "throttling" effect; Table 1). The majority of coronary vascular resistance is in the thick-walled intramural arterioles, since the large, extramural vessels contribute little resistance. Dilatation or constriction of the resistance vessels principally regulate coronary blood flow. Patency of these vessels depends on intravascular pressure and ceases below a critical pressure, the closing pressure, which can be 20 to 30 torr. Coronary blood flow is reduced by decreased diastolic pressures, increased ventricular end diastolic pressures, coronary obstruction, and tachycardia. Coronary obstructions can be either fixed or compliant. With compliant lesions, flow across the lesion can be increased by

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Table 1. *Factors Associated with Perioperative Ischemia/Infarction*

Tachycardia
Hypotension/hypertension
Coronary spasm
Poor ventricular function
Coronary endarterectomy
Multiple coronary lesions/grafts
Left main coronary artery disease
History of previous infarction
Prolonged aortic cross-clamp time
Prolonged cardiopulmonary bypass
Associated renal disease
? Anesthetics (isoflurane, nitrous oxide)

increased driving pressure. Increases in pressure proximal to a fixed obstruction decrease flow across the obstruction.

Myocardial infarction usually occurs with complete occlusion of a coronary artery. It is a gradual process, beginning in the subendocardium and evolving over 9 to 12 hours. Factors affecting infarct size include severity of ischemia and efficiency of anaerobic metabolism.

Within 3 minutes of an ischemic insult, most of the creatine phosphate is lost, adenosine triphosphate (ATP) decreases to 35 per cent of control, but reversibility is still possible. Mitochondrial respiration is inhibited, anaerobic glycosis occurs, and contractile activity ceases. Other metabolic and mechanical aspects of myocardial ischemia are reviewed extensively by Allen and Orchard.[2] Reversibility is assured with reperfusion within 20 to 40 minutes and likely within 4 to 6 hours. Reperfusion of acutely ischemic myocardium modifies infarct size, but also causes reperfusion dysrhythmias, the "no-reflow" phenomen (secondary to endothelial cell swelling), and other postreperfusion damage.

DIAGNOSIS OF ISCHEMIA AND INFARCTION

Intraoperative Diagnosis

Because the anesthetized patient is unable to verbally indicate the presence of angina or other symptoms of myocardial ischemia, other methods are necessary for diagnosis. These methods are discussed in the article by Clements and de Bruijn in this issue. Unfortunately, different diagnostic methods do not always agree that ischemia is present.

Preoperative exercise testing determines the maximal attainable workload and the heart rate-systolic blood pressure product (RPP) at which angina develops. Although RPP is a rough estimate of myocardial oxygen demand, it has significant problems that preclude its routine clinical use as a monitor of ischemia. A potentially more reliable predictor of myocardial ischemia than RPP is the pressure rate quotient (PRQ = mean arterial pressure/heart rate) at least in an experimental animal model.[14]

Electrocardiography

The electrocardiogram (ECG) remains one of the most commonly used and most highly specific methods to diagnose intraoperative ischemia. Accepted ECG criteria for ischemia are elevation or depression of the ST segment by 0.1 mV or more 60 to 80 ms after the J point. T-wave changes alone are insufficient to diagnose ischemia.[41] In addition to ST-segment changes, new left bundle branch block is a reliable sign of intraoperative myocardial damage associated with increases in not only perioperative infarction but also low cardiac output and death.[18]

Both standard and precordial leads should be monitored. Specialized leads such as the CM_5, CB_5, or CS_5 may be used during cardiac surgery or when a multilead system is unavailable. These leads primarily reflect left ventricular ischemia (Fig. 1). In one study intraoperative ischemia was simultaneously demonstrated in II, V_5, CS_5, and CB_5 indicating the usefulness of single bipolar leads.[35]

Ischemia of the right ventricle may significantly impair

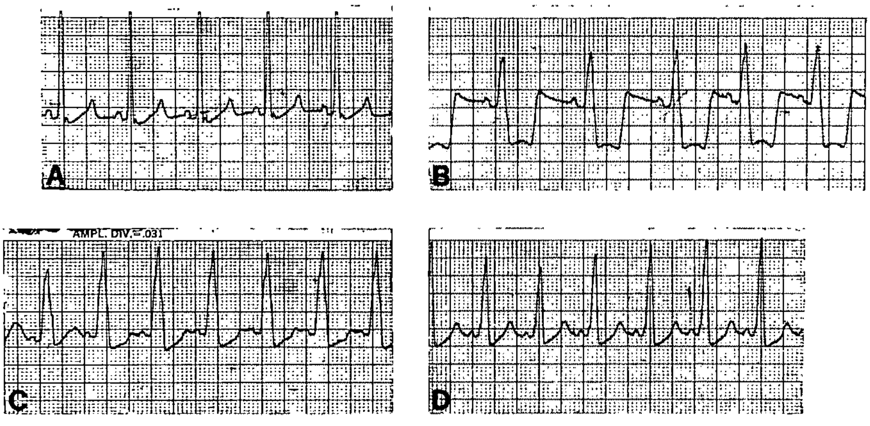

Figure 1. ECG evidence of ischemia in lead V_5. (A) The ECG prior to cardiopulmonary bypass is shown. (B) The ECG shows changes associated with air in the coronary grafts prior to discontinuation of bypass. (C) Partial resolution of ischemia 5 minutes after discontinuation of bypass is demonstrated. (D) Further improvement is shown 60 minutes after bypass.

pulmonary blood flow and left ventricular performance, particularly in the presence of pulmonary hypertension. Electrocardiographic leads V_1, V_{4R}, and CR_{4R} provide an effective view of right ventricular ischemic events. An esophageal lead easily detects ischemia in the posterior left ventricle and right ventricle.[44]

However, many standard ECG systems fail to detect the majority of ischemic episodes.[21,80] Sophisticated microcomputer-based ST-segment trend recorders discussed elsewhere in this issue are necessary to detect more subtle changes.[51] The usefulness of such systems in the early diagnosis of graft occlusion was noted by Kotter and coworkers.[50]

Scintigraphy

Although nuclear imaging using thallium 201 or ^{99m}technetium pyrophosphate is not easily adaptable to the operating room, it is an excellent way to detect ischemia. Myocardial uptake of thallium depends on coronary blood flow and inward movement of thallium into the intracellular compartment and its loss into the blood pool. Transient ischemia is best detected by exercise thallium studies. Changes in wall motion on technetium scanning unassociated with hemodynamic or ECG changes have been reported in a small series of patients by Sell and colleagues during endotracheal intubation.[83] In the postoperative period, 89 per cent of perioperative MI were diagnosed with technetium scanning alone.[61]

Ventricular Filling Pressure

Changes in ventricular compliance and contractility usually accompany myocardial ischemia. Such changes are manifested by increased left ventricular filling pressures detected by an acute increase of 6 to 10 torr in pulmonary artery wedge pressure. The wedge pressure tracing may have prominent A–C or large V waves, resulting from ischemia of the mitral papillary muscles. Mitral regurgitation need not be present, however, as the V waves result from changes in ventricular compliance.

Increased right atrial pressure with a Y descent greater than or equal to the X descent and consistent with the development of a V wave accompanies right ventricular failure secondary to ischemia. The V wave results from either tricuspid regurgitation on the basis of papillary muscle dysfunction or decreased right ventricular compliance.[91] Equality of the right atrial pressure and pulmonary artery diastolic pressure is a frequent occurrence in right ventricular ischemia and infarction.[57] Nevertheless, electrical evidence of ischemia can be present in the absence of changes in pulmonary wedge pressure, possibly resulting from regional rather than global ischemia, which alters ventricular compliance.[51]

Echocardiography

Intraoperative ischemia can be detected by surface or transesophageal echocardiographic determination of regional wall motion abnormalities and ejection fraction. The equipment, methods, and results are discussed in the article by Clements and de Bruijn in this issue.

Metabolic Indicators

Because lactate, phosphate, hypoxanthine, potassium, and inosine are released from the myocardium during ischemia, their release serves as an indicator of ischemia. Release is documented by determination of myocardial extraction of the indicator (the arteriocoronary venous content difference divided by arterial content). Lactate extraction decreases with ischemic ECG changes, although lactate production occurs in only a third of ECG abnormalities.[75] The problem with metabolic indicators is that ischemia in only one portion of the heart may not be reflected by sampling from the coronary sinus. Intraoperative measurements of intramyocardial pH changes during pacing correlate with critical stenosis in the coronary artery supplying the involved myocardium.[45]

Practical Intraoperative Monitors of Ischemia

As demonstrated during percutaneous coronary angioplasty, acute ischemia is heralded by hypokinesia, progressing to dyskinesia begins within 19 ± 8 seconds of coronary occlusion. A shift in the ST segment occurs within 30 ± 10 seconds after occlusion, but angina is absent until 39 ± 10 seconds. Within 17 ± 8 seconds of reperfusion, wall motion normalized.[37] A similar time sequence is noted in canine studies in which abrupt occlusion is characterized by a bulge in the ischemic myocardium during isovolumic relaxation. With gradual coronary occlusion, early systolic lengthening, increased end diastolic length, and postsystolic shortening occur in the myocardium.[24]

The earliest diagnostic indicators of ischemia during cardiac surgery are pulmonary artery wedge pressures and echocardiographic evidence of wall motion abnormalities since ischemia affects both systolic and diastolic function.[16,43] Use of these monitors decreased operative mortality in patients with left main coronary obstruction.[65] However, small areas of myocardium may be ischemic in the absence of changes in either wall motion or filling pressures.

Postoperative Diagnosis

The need for a combination of serial ECG analysis, isoenzyme determination, technetium pyrophosphate scans, and assessment of ventricular function to detect perioperative infarction has been documented by several investigators.[6,92] Use of enzymes (50 per cent), scans (30.8 per cent), and ECG (10 per cent) alone results in a high incidence of false-positive diagnoses of MI.[6,47,92] Combination of information from ECG, echocardiography, ventricular angiography, and enzyme techniques quantitates the size of acutely infarcted myocardium.[15,33]

Electrocardiographic changes often associated with perioperative myocardial infarction include new, persistent Q waves of 0.04 seconds duration or longer or new QS deflections associated with evolution of ST-segment and T-wave changes.[77] The appearance of new bundle branch block, shift of the electrical axis, life-threatening ventricular dysrhythmias, deep T-wave inversions lasting more than 48 hours, and flat ST-segment depressions of greater than 2 mm in left ventricular leads suggest perioperative MI.[77] ST-segment changes can be unreliable perioperatively because of electrolyte imbalance, surgical trauma, acidosis, cardiopulmonary bypass, and pericardial irritation, which produce transient changes.[46] The appearance of Q waves may result from revascularization unmasking old infarcted areas, since about 20 per cent are associated with little detectable myocardial necrosis.[77]

Necrosis of 3 g of myocardium is necessary to scintigraphically identify acute MI.[77] Technetium scans become positive about 12 hours after MI and its uptake is greatest where blood flow has decreased to 20 to 40 per cent of normal.[77] However, false-positive scintigrams result in patients with ventricular aneurysm, breast tumors, cardiomyopathy, bacterial endocarditis, and after cardioversion.

For diagnosis of MI, creatine kinase MB isoenzymes must be more than two SD above the mean of uncomplicated coronary surgical patients in the particular institution.[19,47,77] Enzymes other than CK-MB such as LDH, SGOT are frequently elevated by noncardiac causes. However, reversal of the ratio of LDH_1/LDH_2 may indicate myocardial infarction.[68]

Most reported studies of perioperative infarction during cardiac surgery have used only one or two methods to diagnose perioperative infarction. ECG changes alone result in a 9 per cent false-positive diagnosis of MI.[6] The extensive series of patients reported by Slogoff and Keats used only enzyme and ECG criteria to diagnose perioperative MI.[86,87] The incidence of MI may be falsely decreased by the use of inappropriate criteria and increased by the failure to require electrical, enzymatic, and mechanical evidence of infarction.

INCIDENCE OF ISCHEMIA AND INFARCTION

Ischemia

During either noncardiac or cardiac surgery, the incidence of ischemia (manifested by ST-segment changes) varies from 11 to 38 per cent.[80,86] If both of Slogoff's studies are combined, the incidence is 42 per cent during cardiac surgery.[86,87] In Slogoff's studies, ST-segment depression was present on arrival in the operating room in 313 patients (21 per cent). This exceptionally high incidence raised questions about preoperative preparation and sedation of their patients [59], since subsequent studies demonstrated a 0.3 per cent incidence.[51] In another large study, ischemia reappeared or occurred primarily in 493 patients (21 per cent) from anesthetic induction to initiation of cardiopulmonary bypass.[25] The lowest incidence of ischemia may actually be intraoperatively with higher incidences preoperatively and postoperatively.

Other investigators using ST-segment trend recorders demonstrate a lower incidence of intraoperative ischemia, although factors such as study duration, number of observations, and male-only population may have affected their results.[51] After 6 months of use of an ST-segment trend analyzer, the incidence of intraoperative myocardial ischemia decreased from 17 to 6 per cent.[51]Such devices may alert the anesthesiologists to ischemic episodes producing only subtle changes not seen on conventional ECG.[52]

In Kotter's study ischemia occurred in only 11.9 per cent of patients prior to bypass, but was increased (23.5 per cent) during coronary reoperations. A higher incidence was also present during valve replacement (25.9 per cent) or combined coronary surgery and valve replacement (35.3 per cent).[51] Ischemia was more common in patients with two or more previous MI, hypertension, and increased left ventricular end-diastolic pressure.[51] It was also more likely during skin incision and sternotomy.[86]

Silent Ischemia

Silent ischemia is objective evidence of myocardial ischemia without accompanying angina or its equivalents. It occurs in 16 to 75 per cent of patients with coronary diseases.[41] Such ischemic episodes (without angina) are frequent, occurring 226 times during 33 24-hour periods in 11 patients.[23] In this same population, 52 episodes were associated with angina. Tachycardia was absent in 65 per cent of such episodes. In another study of patients undergoing percutaneous transluminal coronary angioplasty, asymptomatic ischemic episodes (ST-segment deviations for longer than 30 seconds) occurred twice as frequently as symptomatic episodes.[40] Patients with silent ischemia have lower ejection fractions than those without it possibly because of frequent and prolonged ischemic events.[31]

Many of the episodes of silent ischemia occur during sleep where minimal if any hemodynamic change occurs and are likely the result of decreased myocardial oxygen supply.[96] Silent ischemia also occurs during anesthetic induction in as many as 45 per cent of patients.[48] However, in medically treated patients or postoperatively, the presence of silent ischemia correlated significantly with cardiac events such as angina, myocardial infarction, sudden arrhythmogenic death, or need for coronary revascularization by angioplasty or surgery.[25,32] Much of the ischemia occurring after coronary bypass grafting is asymptomatic (silent).

Right Ventricular Ischemia

The exact incidence of right ventricular ischemia during cardiac surgery is uncertain, although there are several case reports of its occurrence[60,91] (Fig. 2). However, the "throttling" of systolic coronary blood flow is less in the thin-walled right ventricle, making ischemia less common. Inferior myocardial infarction caused by right coronary occlusion can be differentiated from left circumflex occlusion by the presence in circumflex disease of ST-segment elevation in two or more inferior

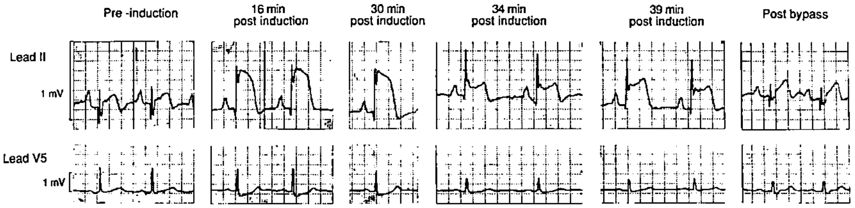

Figure 2. ECG evidence of right ventricular ischemia demonstrating changes in lead II but not in V_5. Improvement in ischemia was associated with coronary vasodilator (nitroglycerin) and vasopressor (phenylephrine) therapy, although residual ST-segment elevation was present after right coronary artery bypass grafting (post bypass panel). (*From* Lynch C: Perioperative right ventricular ischemia. J Cardiothorac Anesth 1:126–131, 1987; with permission.)

leads and ST-segment elevation in one or more lateral leads with an isoelectric or elevated ST segment in lead I.[5]

Ischemia in Surgery for Congenital Lesions

Ischemia is seen infrequently in infants and children undergoing cardiac surgery. Ischemia during surgery for congenital lesions may result from ventriculotomy or coronary air embolism. However, the neonatal myocardium is more dependent on glycolysis causing greater increases in lactate during ischemic episodes.[21] Although some investigators suggest that the neonatal myocardium is more vulnerable, others have demonstrated greater resistance to ischemia.[10,72]

However, ischemia occurs in the absence of coronary occlusive disease in patients with aortic stenosis, hypertrophic cardiomyopathy, and possibly mitral valve prolapse. In the hypertrophied heart, ischemia results from increased myocardial oxygen consumption associated with decreased subendocardial perfusion. Subendocardial perfusion depends on the duration of diastole and the driving pressure for subendocardial flow, which is decreased by the elevated left ventricular pressure and the relatively decreased aortic diastolic pressure.[94]

Infarction

Reported series indicate an incidence of perioperative infarction between 8 and 35 per cent.[6,47,71,76,79,82] Patients having perioperative ischemia episodes during cardiac surgery have an incidence of perioperative infarction of 6.9 per cent.[86] The wide incidence range results from difficulties in the diagnosis of MI after cardiac surgery. The incidence of infarction also correlates with the severity of ST-segment depression in the perioperative period since it was 1.8 per cent with no ischemic changes and 10.4 per cent with greater than 0.2 mV depression.[87] Technical operative difficulties and longer periods of operative aortic occlusion increased the incidence of perioperative MI.[86] In one series with an 8 per cent infarction rate, only 3 per cent were transmural.[15]

ETIOLOGY OF ISCHEMIA AND INFARCTION

Many factors, alone or in combination, are associated with perioperative ischemia and infarction (Table 1). In coronary occlusive disease, ischemia results when adrenergic stimulation increases blood pressure or heart rate, coronary spasm is triggered, or if myocardial oxygen demands exceed supply (as in aortic stenosis).

Factors associated with an increased risk of intraoperative ischemia include hypertension, kidney disease, left ventricular end diastolic pressure over 15 mm Hg, and history of previous infarction.[51] Patients with left main and triple vessel coronary disease are more likely to have perioperative MI.[7] The absence of coronary collateral circulation also predisposes to perioperative infarction.[66] Other risk factors include decreased ejection fraction, increased left ventricular end diastolic pressure, number of coronary grafts, coronary endarterectomy, and prolonged duration of bypass. The incidence of infarction is increased to 50 per cent with three or more risk factors and only 7 per cent with less than three.[7] Patients with reduced ejection fractions are more likely to have a perioperative MI, possibly because increased left ventricular end diastolic pressure decreases subendocardial perfusion.

Anesthesia

The choice of anesthesia may affect either the incidence or severity of ischemia and infarction. In canine experiments, infarct size was increased during barbiturate anesthesia associated with increased heart rates, catecholamines, and lower endocardial/epicardial flow distribution.[42] However, it should be noted that surgical instrumentation requiring thoracotomy was performed 60 minutes before coronary occlusion in the anesthetized group but 7 to 10 days later in the unanesthetized animals.

An early study suggested improvement in ECG signs of ischemia with induction of anesthesia.[26] Kotter and coworkers noted a lower incidence of ischemia with use of both narcotic and hypnotic during anesthetic induction as well as with addition of an inhalation agent (halothane, isoflurane, or enflurane) during narcotic anesthesia.[51] Kleinman and coworkers demonstrated a similar incidence of hypoperfused areas on thallium scintigraphy (it is questionable whether these areas represent ischemia) during induction with either fentanyl or thiopental-halothane anesthesia.[48] The incidence of ischemia during sufentanil anesthesia was 26 per cent using a multichannel continuous ST-segment recording system.[56] The numbers of patients receiving specific anesthetic techniques in most studies of perioperative ischemia is small and their statistical significance questionable.

Early studies with isoflurane demonstrated decreased coronary perfusion pressure and increased coronary sinus blood flow suggesting decreased or little effect on coronary vascular tone.[63] Subsequently, Reiz and coworkers noted a 35 per cent decrease in coronary perfusion pressure with 1 per cent end-tidal isoflurane in patients with coronary artery disease.[74] Coronary vascular resistance, myocardial oxygen consumption, and lactate extraction all decreased. Ten of their 21 patients had ST depression or T-wave inversion, which normalized in two of five patients with improvement in coronary perfusion pressure. In their later study, isoflurane, 1.5 MAC with nitrous oxide, 70 per cent, decreased coronary resistance and great cardiac vein flow.[75] Seven of 13 patients showed ECG evidence of ischemia. However, there are many problems with the study by Reiz et al: (1) patients were unpremedicated; (2) no patients received calcium entry blockers and only a quarter or less were on beta blockers preoperatively; and (3) nitrous oxide and isoflurane are rarely used in clinical cardiac anesthesia in the concentrations used in the study.[74] More recent studies suggest there are fewer unfavorable effects from isoflurane provided high inspired concentrations and hypotension are avoided.[17,88]

Halothane decreases the global myocardial damage from ischemia.[8] However, halothane produces postsystolic shortening in myocardium served by a stenotic coronary artery. With stenoses of increasing severity, paradoxical lengthening during systole occurs. These findings suggest that halothane might produce ischemia in the presence of coronary occlusive disease.[58]

Both coronary steal and regional dysfunction could also occur with enflurane.[22] Regional myocardial dysfunction occurs in areas supplied by stenotic coronary areas in the presence of nitrous oxide.[64,70] Unfortunately, the relevance of experimental animal studies to humans undergoing coronary revascularization is unclear (see articles by Tinker and Hill and Reves in this issue).

Hemodynamic Changes

Although ischemia can occur without hemodynamic changes, particularly during endotracheal intubation,[48] ischemia is often associated with hypertension, tachycardia, and other disturbances.[51,55,80,86] Not all hemodynamic disturbances, however, are associated with ischemia.[95] Part of the problem may be the difficulty in the definition of hemodynamic alterations, since major changes occur within the range accepted as normal by some investigators (heart rate over 100 bpm, systolic BP over 180 mm Hg or under 90 mm Hg were considered abnormal).[59,86]

Heart Rate. Tachycardia increases myocardial oxygen demand and is particularly deleterious to the patient with coronary artery disease who cannot increase oxygen supply. Boudoulas et al demonstrated that the relationship between heart rate and the diastolic portion of the cardiac cycle is nonlinear.[9]

Small increases in heart rate produce dramatic reductions in diastole. In the study of Slogoff and colleagues, the anesthesiologist whose patients had the highest perioperative infarction rate had the highest frequency of tachycardia and ischemia intraoperatively.[86] Other investigators corroborate the association between intraoperative ischemia and perioperative MI.[27] The importance of diagnosis and management of tachycardia cannot be overemphasized when 77.5 per cent of ischemic events were associated with an increase in heart rate of 10 per cent over control and 30 per cent occurred with heart rates exceeding 100 beats per minute.[51]

Changes in ventricular pressure (compliance), volume, or both due to altered diastolic function with ischemia (suggests both myocardial failure and altered diastolic function) occur with tachycardia.[81] Although coronary blood flow increases during tachycardia, the ratio of subendocardial to epicardial blood flow may be reduced. Tachycardia, more than hypertension, enhances development of ischemia.

Blood Pressure. Although increased blood pressure increases myocardial wall tension, a determinant of myocardial oxygen demand, experiments in animals fail to demonstrate a single value of either blood pressure or heart rate that is associated with ischemia. The threshold for ischemia induced by tachycardia depends on pre-existing blood pressure. When the pressure-rate ratio exceeds 1, ischemia is absent even in the presence of coronary stenosis.[13] Lieberman and coworkers noted that either hypotension to less than 65 mm Hg or heart rates over 80 bpm were both associated with ischemia.[55]

Anemia. Although the hematocrit is an important determinant of myocardial oxygen supply, canine experiments demonstrate that ischemia (produced by coronary occlusion) is not increased by hemodilution to hematocrit of 6 per cent[97] because flow through coronary collaterals increases to maintain perfusion. However, the translation of these results from dogs with normal coronary arteries to humans with coronary occlusive disease may not be justified.

Coronary Spasm

Coronary spasm (Prinzmetal's angina) results from an abnormal vasoconstrictor stimulus or arterial hypersensitivity to vasoconstriction.[28,73] Focal endothelial injury with loss of normal endothelial function (release of endothelial relaxing factor) allows blood-born mediators of vasoconstriction to arrive at a vascular area with increased sensitivity. Beta adrenergic blockers often exacerbate coronary spasm. Unlike ischemia produced by fixed coronary lesions, coronary spasm causes ST-segment elevation during the episode.

Inadequate Myocardial Preservation

Hypothermic potassium cardioplegia seems to be associated with decreased perioperative myocardial infarction. The incidence was 13.7 per cent with intermittent aortic clamping without cardioplegia in one series.[34] Perioperative MI is increased with prolonged duration of aortic clamping in several series.[34,76,92] The conditions during cardiac reperfusion are also important. Control of perfusion pressure, flow, calcium ion, pH, and other variables may decrease ischemia during initial reperfusion. Thomson and coworkers report a 43 per cent incidence of ST-segment elevation during reperfusion after 54 minutes of multidose potassium cardioplegia.[89] The duration of ST-segment elevation was about 25 minutes. Right ventricular ischemia seemed particularly likely since ST-segment changes occurred in lead II. Patients exhibiting ST-segment elevation on reperfusion had higher CK-MB, indicating greater myocardial damage.[89]

METHODS OF PREVENTION OF ISCHEMIA AND INFARCTION

Increased preload, afterload, contractility, or coronary spasm cause intraoperative ischemia. Perioperative management must be planned to prevent, limit, or control changes in these variables. Specific methods include the use of intravenous beta blockers such as esmolol to control heart rate, controlled myocardial depression with anesthetic drugs such as halothane, enflurane, and isoflurane, and maintenance of optimal preload and afterload with vasodilator therapy. An increased concentration of oxygen should be administered as oxygen decreases ECG evidence of ischemia and the extent of myocardial necrosis.[61,62]

However, prophylactic use of nitroglycerin 0.5 μg per kg per minute failed to prevent intraoperative ischemia during fentanyl-pancuronium anesthesia in patients having coronary bypass grafts.[90] The patients in Thomson's study were not receiving calcium entry blockers and their beta adrenergic blockage had been terminated at least 8 hours preoperatively. Both heart rate and blood pressure were increased in ischemic as compared with nonischemic patients.

Prophylactic use of diltiazem in a series of patients with coronary disease undergoing noncardiac vascular surgery also failed to prevent intraoperative ischemia. As with Thomson's study of nitroglycerin,[90] ischemia during diltiazem infusion was associated with increased heart rate and blood pressure.[30]

The technique of myocardial preservation should include both topical hypothermia and cardioplegia coupled with myocardial temperature mapping to ensure adequate distribution of cardioplegia beyond coronary stenoses. When ST-segment elevation is seen during reperfusion after aortic occlusion, efforts should be directed to increasing perfusion pressure, coronary vasodilation with nitroglycerin, effective left ventricular venting, removal of intracoronary air, and prolongation of cardiopulmonary bypass.[89]

METHODS OF MANAGEMENT OF ISCHEMIA AND INFARCTION

The goal is to limit ischemia and to prevent infarction. However, it remains unproven that intraoperative detection and treatment of ischemia reduces perioperative cardiac morbidity during cardiac surgery. Single, brief episodes of ischemia are well tolerated in experimental animals. However, multiple episodes may be cumulative, causing release of CPK,[29] and morphologic evidence of necrosis. Other investigators have not always found an association between CK release and myocardial necrosis.[39] Likewise, the absence of CK release does not always prove that small areas of myocardial necrosis have not occurred. Tachycardia, hypertension, hypotension, coronary spasm, increased preload or afterload must be effectively controlled (Table 2).

Tachycardia is managed by identification of the rhythm fol-

Table 2. *Management of Perioperative Ischemia During Cardiac Surgery*

INCITING FACTOR	THERAPY
Tachycardia	Beta blockade
Increased preload	Nitroglycerin
Increased afterload	Increased anesthetic depth ± addition of isoflurane, enflurane, halothane to anesthetic, vasodilators
Hypotension	Decreased anesthetic depth, increased IV fluids ± vasopressors
Decreased contractility	Positive inotropic drugs, intra-aortic balloon
Coronary spasm	Nitroglycerin, sublingual nifedipine, IV verapamil

lowed by specific antidysrhythmic therapy. Supraventricular dysrhythmias such as atrial flutter, fibrillation, or tachycardia require cardioversion, beta or calcium entry blockade, or digitalization to control ventricular response if conversion to normal sinus rhythm is impossible. For sinus tachycardia, particularly when associated with ventricular dysrhythmias unresponsive to lidocaine, beta blockade rapidly controls both dysrhythmias and heart rate. Small doses of propranolol, 0.1 mg per kg, are effective. However, the short-acting beta blocker esmolol in a bolus dose of 1 mg per kg followed by an infusion is more advantageous than longer-acting drugs such as propranolol and labetalol. Beta blockade has been effective in limiting infarct size in medical patients.[69] Recent canine experiments document less lactate production with esmolol administration (150 μg per kg per minute) prior to left anterior descending coronary occlusion for 15 minutes.[85] The adverse hemodynamic effects of coronary occlusion were also alleviated by esmolol therapy.[85]

Increased preload, unassociated with systemic hypertension, is easily controlled with nitroglycerin. Systemic hypertension requires determination of etiology and prompt control with additional anesthesia and/or arteriolar vasodilation. Hess and coworkers suggest that isoflurane is more efficacious than halothane to control intraoperative hypertension during coronary surgery because it produces less myocardial depression while substantially reducing systemic vascular resistance.[38] The treatment of hypotension may require volume expansion, decreased anesthetic depth, and occasionally peripheral vasoconstriction with alpha agonists. Ischemic changes on ECG unassociated with hemodynamic alterations can be controlled with nitroglycerin, sublingual nifedipine, intravenous verapamil, or decreased preload, afterload, and contractility.

Coronary spasm in the perioperative period may present in the classical fashion with ST-segment elevation. However, sudden unexplained hemodynamic collapse also occurs.[49] Intravenous nitroglycerin alone or coupled with sublingual nifedipine (10 mg) relieves spasm and improves coronary flow and hemodynamic variables. Intravenous verapamil is effective in refractory cases.[67] After such episodes, continuous pharmacologic support to prevent further episodes is warranted.

Spasm occurs in internal mammary arteries and saphenous vein grafts as well as native coronary arteries.[93] Immediately after operative removal, veins react to endogenous vasoactive substances (thromboxane A_2, norepinephrine, etc).

OUTCOME AFTER PERIOPERATIVE ISCHEMIA AND INFARCTION

Resolution of ischemia is often accompanied by dysfunctional "stunned myocardium" rather than normal myocardial function. Derangement of cellular energy processes depends on the duration and intensity of the ischemic episode.

Significant myocardial reserve often allows myocardial injury, particularly in the subendocardium, to be clinically and electrically silent. Indeed the ECG manifestations of ischemia may be predictive of outcome. In a recent study of patients presenting for admission to coronary care units because of acute myocardial ischemia at rest, the presence of ST-segment elevation signified a patient population at greater risk for acute myocardial infarction, life-threatening dysrhythmias, and cardiac death. Other manifestations such as ST-segment depression or T-wave changes were unassociated with these risks.[84]

Heart failure and hypotension were significantly more frequent in patients with perioperative MI.[11,54,92] Whether or not coronary bypass grafts remain patent in the presence of perioperative MI is unclear.[1,43] Burton and colleagues report three times the rate of graft occlusion in patients with perioperative infarction compared with those without infarction.[15]

Other investigators note that perioperative MI is frequently benign.[6,15,78] The long-term effects of perioperative infarction are uncertain with some investigators noting decreased survival, reduced exercise tolerance, and ventricular ejection fractions[1,66,78] while others note no difference.[15,34]

Concern over the effects of inotropic support on the ischemic heart is always present when heart failure results from perioperative MI. However, canine experiments demonstrated that dopamine increased contractility without reduction of myocardial high energy phosphate stores, increased infarct size, or deterioration of myocardial function when perfusion was present.[3]

In animal experiments, pulsatile left atrial-femoral artery bypass that completely unloads the left ventricle limits the size of infarction resulting from acute ischemia.[36] Ventricular assist devices and intra-aortic balloon counterpulsation may help to salvage ischemic myocardium by providing similar benefits to prolonged cardiopulmonary bypass.

In canine experiments postsystolic shortening during coronary occlusion was present to the greatest extent in the least ischemic segments, which were most likely to recover on reperfusion. Post-systolic shortening and thickening (the magnitude of segment shortening and wall thickening occurring after end systole) immediately before coronary reperfusion correlated with the magnitude of maximal recovery of systolic shortening after reperfusion.[12] This finding is a potentially useful indicator of functional recovery in humans subjected to early reperfusion during MI.

Careful control of the conditions for reperfusion of hearts after prolonged episodes of ischemia (6 hours) results in functional recovery and salvage of myocardium. Optimum conditions for reperfusion under these circumstances have been outlined by Buckberg[53] and are certainly applicable during cardiac surgery. Methods include reperfusion during total cardiopulmonary bypass with ventricular decompression, pressure of 50 torr, regional cardioplegia, and normothermia for at least 20 minutes. Components of the reperfusion solution include glucose, free radical scavengers, osmotic agents, buffer, amino acid precursors, Kreb's cycle intermediates, oxygen, potassium, and membrane stabilizers.[53] Addition of a calcium channel blocker or use of a hypocalcemic solution is recommended to reduce entry of calcium into ischemic cells.

SUMMARY

Ischemia and infarction occur during all types of cardiac surgery although they are more common during coronary artery surgery. They result from hemodynamic changes causing imbalance between myocardial oxygen supply and demand, coronary artery spasm, coronary air embolism, and technical problems associated with attempted revascularization. Coronary perfusion must be improved if MI is to be avoided. Measures to alleviate ischemia include pharmacologic therapy with nitroglycerin, calcium entry blocking drugs, and vasodilator therapy to control preload or afterload, skillful anesthetic management to minimize oxygen supply/demand imbalance, and controlled prompt reperfusion.

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Perioperative Ischemia and Infarction: Noncardiac Surgery

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Numerous recent advances in our knowledge of coronary artery disease (CAD) necessitate changes in the anesthesiologist's approach to perioperative myocardial ischemia and myocardial infarction (MI). Notably, the recent characterization of silent myocardial ischemia[8] (asymptomatic ischemia, which is diagnosed by electrocardiographic changes or myocardial wall motion abnormality) suggests that the previously reported prevalence of CAD substantially underestimates the true size of the population at risk for perioperative ischemia and MI. The anesthesiologist caring for patients undergoing noncardiac surgery can be certain the patient has CAD if there is a definitive diagnosis of MI viz an event proven by documented cardiac enzyme elevations and diagnostic electrocardiographic changes. In addition, patients who have had recent cardiac catheterization, previous coronary artery bypass grafting surgery or percutaneous transluminal coronary angioplasty (PTCA) also present no difficulty regarding identification of the presence of CAD. The magnitude of ischemia risk is less certain for patients who lack a definitive diagnosis of CAD and present for surgery and anesthesia with a vague history of chest pain, or are taking antianginal medications for unclear reasons or have an inconclusive preoperative cardiology consultation. The routine 12-lead ECG may have equivocal findings suggestive of CAD. In addition, a substantial number of patients who have no signs or symptoms of CAD but actually have the disease will be anesthetized and undergo surgery.

Although the presence of CAD risk factors (family history,

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hypertension, smoking, hyperlipidemia, diabetes) in addition to age and gender factors, may place the patient in a risk category for asymptomatic CAD, the precise epidemiology of silent myocardial ischemia in the surgical population is unknown. It has been estimated that 1 to 2 million middle-aged males have asymptomatic CAD.[9] As many as 900,000 patients undergoing anesthesia and surgery each year have been calculated to have CAD and therefore to be at risk for perioperative myocardial ischemia and MI.[39] Another population of patients experiencing myocardial ischemia that is not due to atherosclerotic disease but secondary to coronary artery spasm may contribute to perioperative morbidity and mortality. Thus, although the majority of myocardial ischemia does not result in MI, the presence of unsuspected CAD requires that improved methods of perioperative ischemia detection be developed for noncardiac surgical patients in order to reduce the incidence of postoperative MI.

PREOPERATIVE DIAGNOSIS OF CORONARY ARTERY DISEASE AND OUTCOME

In order to determine the predictive value of preoperative CAD tests, studies have related the results of the preoperative resting 12-lead electrocardiogram, exercise electrocardiography (treadmill), and radionuclide scanning techniques, including dipyridamole-thallium imaging, with the incidence of perioperative cardiac events. These have been exhaustively reviewed.[39,52]

Although exercise electrocardiographic testing has proved useful for the detection and functional evaluation of CAD, compared with standard 12-lead resting ECG, it does not appear to add significantly to cardiac risk prediction in elderly patients undergoing noncardiac surgery.[8] Other studies in vascular surgery patients suggest that exercise electrocardiography does have predictive value regarding perioperative cardiac events.[14,62] Therefore, in suitably selected patients, this test may contribute to risk prediction in patients in whom CAD is suspected on the basis of history, CAD risk factors, or equivocal resting 12-lead ECG results. However, its sensitivity as a predictor of cardiac risk in this patient population has not been compared with coronary angiography. Furthermore, exercise testing is frequently impractical in potentially high-risk patients such as those with advanced peripheral vascular disease.

In order to evaluate the severity of suspected CAD without performing coronary angiography, the use of dipyridamole to induce coronary vasodilatation prior to thallium scintigraphy with immediate and delayed imaging has been investigated.[6] Regional myocardial uptake of thallium is related to blood flow; a normal scan shows no thallium defects and an abnormal scan demonstrates perfusion defects in the immediate images or areas with increased thallium concentration on the delayed images. This latter phenomenon, thallium redistribution, is a marker for hypoperfused, jeopardized, but viable myocardium. A persistent thallium defect suggests the presence of an infarcted or scarred area. Although precise correlation with preoperative clinical factors[27] was not demonstrated,[41] this technique clearly has important predictive values. It is considered safer than coronary angiography and may aid in the selection of patients at high risk for postoperative cardiac events who would have improved outcome with initial coronary revascularization. In a validation study, dipyridamole-thallium imaging had similar sensitivity and specificity compared with selective preoperative clinical factors.[18] However, the technique has been shown to have superior predictive value compared with exercise ECG testing. Although dipyridamole-thallium testing is not without complications (for example, exacerbation of myocardial ischemia), it has the advantage of being relatively noninvasive and can be performed in patients in whom exercise testing is impractical.

Certainly, better selection of patients is necessary to improve postoperative cardiac outcome by performing timely surgical or nonsurgical (PTCA) coronary artery revascularization prior to any necessary noncardiac surgery.

ST-SEGMENT MONITORING

Increasing evidence that the majority of myocardial ischemia is both transient and asymptomatic[15,22] has accompanied important technical advances in electrocardiographic monitoring. Computer analysis of standard and signal-averaged high-frequency electrocardiograms improves the sensitivity of ischemia detection and may aid in the diagnosis of chest pain of uncertain etiology.[1] More importantly, the application to myocardial ischemia detection of real-time, digitized and continuous ECG monitoring is providing significant new information.[36] Continuous ECG monitoring in ambulatory patients permits the diagnosis of unrecognized or unsuspected myocardial ischemia. Improvements in the quality of ST-segment analysis permit continuous, faithful reproduction and storage of ST-segment data, which can then be readily retrieved for precise characterization of ischemic episodes.[15] Validation studies of new solid state recorders that analyze digitized ECG and display ST-segment depression, demonstrate both sensitivity and specificity for ischemia of greater than 90 per cent when compared with standard Holter recordings[4,31] (see article by Clements and de Bruijn in this issue).

SILENT MYOCARDIAL ISCHEMIA

What is the nature of silent myocardial ischemia? Exercise studies in patients with angiographically documented CAD demonstrate that ECG evidence of ischemia without associated angina is common.[2] Furthermore, there appears to be no significant difference in the characteristics of patients with asymptomatic ischemia compared with those with angina: age, sex, history of MI, heart rate, maximal ST-segment depression, extent of CAD, and left ventricular ejection fraction are all similar. What is the outcome and natural course of asymptomatic CAD? Overall, the prognosis of asymptomatic CAD is less favorable than was initially thought to be the case.[10] Patients with silent myocardial ischemia, three-vessel disease, and poor exercise tolerance may go on to sudden death or MI. Furthermore, silent ischemia occurs in greater than 50 per cent of patients with unstable angina, in spite of intensive medical treatment.[28] Silent ischemia identifies patients with unstable angina who are at high risk for the early occurrence of unfavorable cardiac events. The majority of postinfarction ischemia appears to be silent and these events are significantly correlated with 1-year mortality.[29] Similarly, it appears that the early onset of silent ischemia following coronary artery bypass grafting is associated with a high incidence of cardiac events in the first year.[20]

It has been shown in animal studies that intermittent brief periods of ischemia have a cumulative effect and can lead to myocardial necrosis.[25] Both the duration and frequency of ischemic events in humans may compound to contribute to what has been termed "the total ischemic burden."[11] The temporal sequence of myocardial ischemia manifestations suggest that an initial imbalance in myocardial oxygen supply and demand leads first to diminished ventricular compliance (diastolic dysfunction) followed by decreased myocardial contractility (systolic dysfunction) and increases in left ventricular end-diastolic pressure.[45] Subsequent to wall motion abnormalities, ST-segment abnormalities appear and only later and infrequently does angina arise.

CONTINUOUS PERIOPERATIVE ST-SEGMENT MONITORING

Intraoperative Holter monitoring in noncardiac surgical patients has demonstrated that ischemia is common at induction, during surgery, and at extubation and emergence from anesthesia.[12] We have used continuous electrocardiographic monitoring for ST-segment and heart rate measurement in the preoperative, intraoperative, and postoperative phases of noncardiac surgery. Preliminary findings from these studies suggest that perioperative ischemia occurs predominately in the postoperative period and is most commonly asymptomatic and associated with increases in heart rate (unpublished data). In patients with CAD, ischemia may occur when heart rate increases by as little as 5 per cent above resting nonischemic levels, although a 20 per cent increase is more commonly the threshold for ischemia. Thus, a heart rate of 110 minute^{-1}, a suggested ischemia threshold during coronary artery bypass surgery,[56] cannot be generally applied as a predictor of ischemia onset.

In spite of medical therapy, patients with CAD have frequent preoperative episodes of myocardial ischemia in the period immediately (2 days) prior to undergoing coronary artery revascularization.[34] Preoperative silent myocardial ischemia may have predictive value with regard to the occurrence of postoperative cardiac events in noncardiac surgical patients. It has been recently demonstrated that mental stress is an important determinant of transient silent myocardial ischemia.[53] The perioperative period is characterized by numerous events that may produce sufficient mental stress or pain to result in myocardial ischemia (Table 1). In this regard, there is evidence that both blood pressure and heart rate increase in the immediate preoperative period.[24] Preoperative stress is associated with an increase in epinephrine and anxiety prior to the induction of anesthesia.[23] Preoperative ischemia may identify a surgical population that would benefit from immediate postoperative therapeutic intervention, especially with regard to the prevention of increases in heart rate. It may also select patients with unsuspected CAD for further preoperative diagnostic and therapeutic measures.

Table 1. *Stressful Perioperative Events (Pain and Anxiety)*

PREOPERATIVE	INTRAOPERATIVE	POSTOPERATIVE
Admission procedures	Intubation	Emergence from anesthesia
Venipuncture	Incision, surgical manipulations	Surgical pain
Diagnostic tests	Endotracheal suctioning	Physiotherapy
Physician visits	Pharyngeal suctioning	Ambulation
Premedication	Extubation	Removal of tubes and drains
Transportation to operating room		
Vascular cannulation		

RISK FACTORS AND OUTCOME EVENTS (ISCHEMIA AND INFARCTION)

The incidence of postoperative MI in patients without documented CAD was estimated at 0.1 per cent in 1972.[58] Risk estimation is complicated by the presence or absence of independent factors such as history of MI, time elapsed since previous MI, congestive heart failure, type of procedure, and age. The various risk factors for postoperative MI, in estimated descending order of importance, are listed in Table 2. Increased heart rate is a major determinant of perioperative ischemia. Angina, dysrhythmia, diabetes mellitus, and age have also been reported as risk factors but are not well supported in the literature.

Although perioperative ischemia is common in patients with CAD, it only infrequently leads to dire events as shown in Table 3. The incidence of ischemia in noncardiac surgical procedures ranges from 20 to 40 per cent, which appears similar to the incidence of ischemia in patients having cardiac surgery. Only about 8 per cent of patients with intraoperative ischemia have an infarct: 92 per cent of patients with ischemia do not have infarction.

The incidence of MI following noncardiac surgery is shown in Tables 3 and 4. The wide variability in reported in-

Table 2. *Risk Factors for Postoperative Myocardial Infarction Following Noncardiac Surgery*

RISK FACTOR	REFERENCE
Recent myocardial infarction	50, 57, 58
Evidence of congestive heart failure	
Decreased ejection fraction	46
By history	27, 50
Intraoperative increases in heart rate	50
Intraoperative hypotension	40, 50, 57
Hypertension	50, 57

Table 3. *Incidence of Intraoperative Ischemia and Perioperative Infarction for Various Surgical Procedures*

	INCIDENCE OF ISCHEMIA (%)	INCIDENCE OF INFARCTION (%)	INFARCTION LEADING TO DEATH (%)	REFERENCE
CABG	37–45	6.9*	36–46	
		2.5†		55, 32
Abdominal aortic aneurysm	22	10*	80–86	7, 51
General	38 with CAD	9*		54, 58
	0 without CAD	0†		
Carotid endarterectomy	43	3.2*	42–50	3, 13, 59, 19
Distal aortic procedures	40	0*		
		0†		12

* After ischemia.
† Without ischemia.

cidence reflects, inter alia, the effects of both time and study population. The table suggests an improvement over time of MI outcome (mortality). All studies of morbidity and mortality must be interpreted in light of the limitations of standards of care prevailing at the time of the research. For instance, in 1961, the ECG was the only reliable diagnostic measure of MI. The diagnostic importance of serum enzymes was not established and isoenzyme and radionuclide methods for MI detection were not available. Thus, the low mortality from MI reported in 1961 may reflect the insensitivity of MI diagnosis rather than better outcome.

In addition to MI detection methodology, anesthetic techniques and agents have improved. Also, major advances in the preoperative medical therapy of CAD with the use of vasodilators, beta-blockers, calcium entry blockers, and antiplatelet agents have favorably influenced the incidence and outcome of perioperative MI. Intraoperative monitoring techniques have changed substantially since 1961. The study by Rao et al[50] suggest that invasive monitoring techniques, aggressively applied and followed by aggressive intervention, may reduce the incidence of perioperative MI.

Driscoll et al (1961)[17] made two observations that have been substantiated by subsequent investigations. First, the surgical site influences the incidence of cardiac events[50,57] and second, MI is more frequent in patients experiencing intraoperative hypotension.[40,57] In 1972, the diagnosis of postoperative reinfarction was established by clinical symptoms, ECG, cardiac enzymes, or postmortem examination.[58] In this study, pre-

Table 4. *Postoperative Myocardial Infarction Following Noncardiac Surgery*

YEAR	RISK FACTORS IDENTIFIED	INCIDENCE OF INFARCTION (%)	MORTALITY FROM INFARCTION	OTHER FACTORS INCREASING RISK	FACTORS NOT INCREASING RISK
1961	Hypotension	4.5	NR		
	No hypotension	2.0	NR		
(Driscoll)			Overall 17%		
1972	Previous MI			Surgical site	Duration, type of anesthesia
(Tarhan)	All	6.6	54%		
	0–3 months	37	NR		
	4–6 months	16	NR		
	>6 months	5	NR		
	No previous MI	0.13	69%		
			Overall 62%		
1978	Previous MI			Postoperative hypertension, intraoperative hypertension or hypotension, surgical site and duration	Diabetes, sex, age, type of anesthesia
(Steen)	0–3 months	27	NR		
	4–6 months	11	NR		
	>6 months	5	NR		
			Overall 69%		

1981 (von Knorring)	Previous MI	15	30%		Diabetes, preoperative hypertension, surgical site and duration
	No previous MI	0.1	50%		
	Hypotension	21	NR		
	No hypotension	6	NR		
			Overall 36%		
1983 (Rao)	Previous MI			Intraoperative hypertension or hypotension, tachycardia, surgical site, preoperative congestive heart failure	
	0–3 months	5.8	NR		
	4–6 months	2.3	NR		
	>6 months	1	NR		
			Overall 36%		
1985 (Pasternak)	Ejection fraction				Surgical site, age
	>56%	0	0%		
	36–55%	19	13%		
	>35%	75	17%		
			Overall 14%		

NR = not reported; MI = myocardial infarction; Overall refers to mortality of all patients regardless of risk factors. See text for detailed discussion vious MI was identified as a risk factor and postoperative reinfarction occurred most frequently on the third postoperative day. Von Knorring reported that 87 per cent of postoperative MIs occurred within 3 days after surgery.[63]

What are the characteristics of postoperative reinfarction? In 1978, Steen reported that recent MI significantly increased the risk of reinfarction.[57] The incidence of reinfarction was also increased by preoperative hypertension, intraoperative hypotension, prolonged surgery, and abdominal or intrathoracic surgery. No particular anesthetic was associated with an increased incidence of MI, an important observation that suggests that method was more important than drug selection. More recently, a substantial improvement in the incidence of reinfarction has been reported (Table 4).[50] Hemodynamic monitoring in this study included a radial artery catheter for the direct measurement of blood pressure and pulmonary artery catheter for cardiac output and pulmonary artery wedge pressure measurements. Cardiovascular variables were controlled within ±20 per cent of baseline measurements. Reinfarction was two to four times more frequent in patients having upper abdominal and intrathoracic procedures, confirming the importance of the operative site. Patients having a nitrous oxide-oxygen narcotic anesthetic were more likely to reinfarct than those who received inhalation agents or those who did not receive nitrous oxide. A 1985 study using radionuclide angiography further delineates the risk of perioperative MI. Patients with an ejection fraction greater than 55 per cent did not have perioperative MI, despite the fact that 20 per cent of these patients had a previous MI.[46] Thus, further developments in diagnostic and prediction methodology have refined the subject of cardiac risk in noncardiac surgery patients.

There appears to be a decreasing trend in both the overall incidence and the mortality of perioperative MI. Improvements in the medical preparation for surgery, surgical and anesthetic techniques, selectivity of cardioactive agents, the sensitivity and specificity of intraoperative cardiovascular monitoring, and the diagnosis and therapy of MI all contribute to this.

DIAGNOSIS OF POSTOPERATIVE MYOCARDIAL INFARCTION

The sensitivity and specificity of current MI diagnostic tests are shown in Table 5. Creatine kinase isoenzyme, muscle band (CK-MB) fraction is a sensitive but potentially nonspecific

Table 5. *Sensitivity and Specificity of Tests for MI*

	EKG (%)	TECHNETIUM SCAN (%)	LDH ISOENZYMES AND CK-MB (%)	THALLIUM SCAN (%)	REFERENCE
Sensitivity	67	75–95	86–100	58–100	33, 5, 48
Specificity	100	64–97	68–96	63–88	60, 33, 63

test because of its release by tissues other than cardiac muscle during surgery. Levels greater than 5 per cent (of total CK) have been reported following transurethral resection of the prostate, cesarean section, and gastrointestinal resection. However, the CK-MB level is usually low and only transiently elevated in these cases. If the CK-MB exceeds 5 per cent 24 hours after noncardiac surgery, MI is highly probable.[5] The 12-lead ECG may be falsely negative or equivocal in up to a third of patients; ischemic changes may not be detectable in patients with conduction abnormalities or pacemakers.[60] Technetium 99 scans become positive 6 to 12 hours after infarction, but the true-positive yield for MI diagnosis is maximal at 24 to 72 hours postinfarction. Thallium scanning within 6 hours of infarction is 100 per cent sensitive for infarction, within 10 hours 88 per cent sensitive, and within 24 hours the sensitivity is only 58 per cent.[48] False-negative results may occur in the setting of subendocardial infarction and with unstable angina. An immediate scan is nonspecific, but specificity improves to 88 per cent at 10 hours.[63] Because of the limitations in the interpretation of these tests, the diagnosis of MI is significantly improved when two or more diagnostic criteria are applied.[60]

TREATMENT OF PERIOPERATIVE ISCHEMIA

The treatment of intraoperative myocardial ischemia has recently been reviewed,[42] is summarized in Table 6, and is the subject of articles by Leone and Kaplan in this issue. Important principles of management have been derived from clinical and

Table 6. *Treatment of Intraoperative Ischemia*

CONDITION	INTERVENTION
Increased heart rate	Anesthesia ± beta blocker
Increased pulmonary artery pressure	Nitroglycerin
Decreased blood pressure	Phenylephrine
ST-segment change only	Nitroglycerine ± calcium blocker

laboratory investigations that have clarified the factors that precipitate ischemia. Of major importance is the growing body of data that suggests that a substantial component of the ischemic burden is unrelated to hemodynamic variations from values that are not associated with ischemia.[15,34,55,56] Thus, as more sensitive ischemia detection methodology has developed, a new aspect of the disease has emerged that is not subject to the traditional therapeutic objectives of normalizing heart rate, coronary perfusion pressure, and pulmonary artery pressure. This type of ischemia appears to result from an impairment in myocardial oxygen supply due to either coronary artery spasm or platelet aggregation compounding partial occlusion due to pre-existing atheroma.[42] In spite of this, it is probable that careful attention in the perioperative period toward the prevention of increases in heart rate, especially in the presence of decreased blood pressure, will prevent the majority of ischemic events.

PREVENTION AND TREATMENT OF INCREASES IN HEART RATE

Preoperative Period

Increases in heart rate that may be associated with anxiety-provoking events are summarized in Table 1. These may be prevented by appropriate reassurance and supportive psychologic measures in addition to the use of sedative, hypnotic, analgesic, and anxiolytic pharmacologic agents. Although the effect of different premedication regimens on preoperative heart rate and ischemia has not been evaluated, this may contribute to the difference in new ischemia observed in patients arriving in the operating room for coronary artery bypass surgery.[34,55]

Pharmacotherapy aimed at controlling heart rate, notably the use of beta-blocking agents, should be optimized in the preoperative period. The minimum requirement is that beta-blocker medication be continued until the time of surgery. Unfortunately, as discussed previously, a substantial number of patients who present for noncardiac surgery will have unsuspected CAD and others with CAD will not be receiving the benefit of beta blockade because of noncompliance or withdrawal of the drug due to side effects. In these patients, the skillful and conscientious reduction of anxiety and pain prior to induction of anesthesia may prevent increases in heart rate and ischemia.

The benefits of beta-blocker therapy in patients with myocardial ischemia in the nonsurgical population have been convincingly demonstrated.[30] In the noncardiac surgical population, the use of preoperative metoprolol in patients undergoing elective abdominal aortic aneurysm repair and its continuation during the postoperative period is associated with favorable hemodynamics and perhaps a reduction in perioperative myocardial events; a historical control group was used.[47] Although vasodilator therapy in the preoperative period has been shown to eliminate ischemia in patients undergoing coronary artery bypass surgery,[65] treatment with calcium entry blocking drugs in this population does not appear to reduce new preoperative ischemia.[55] The absence of an effect of calcium entry blockers in this context is somewhat surprising in view of the clear importance of this therapy in other patients with myocardial ischemia.[26,44] This may reflect methodology, particularly in regard to the use of noncontinuous detection of ischemia.

Intraoperative Heart Rate Control

The potentially stressful event of intubation and prevention of associated increases in heart rate and blood pressure have been thoroughly investigated beginning with the pioneer work of Prys-Roberts. However, with the immediate preinduction use of potent narcotics (fentanyl, sufentanil) and the careful avoidance of tachycardia (including avoidance of pancuronium) at this time of surgery, it may well be that intubation is of decreasing importance vis-à-vis the precipitation of myocardial ischemia. It is possible that extubation and emergence from anesthesia in the presence of a decreasing level of general anesthetic may be associated with more important increases in heart rate and associated cardiac events.[43] Obviously, depth of anesthesia is the major difference between these two times: it can be deep for induction but must be light for emergence.

The treatment of new onset intraoperative ischemia is summarized in Table 5 and depends on accurate diagnosis. In this regard the use of a digitized display of ST-segment trend is of great value and should be applied to noncardiac surgical patients who are at risk, as discussed previously, for intraoperative ischemia.

Postoperative Control of Heart Rate

It has been known for some time that the most common perioperative time for the occurrence of MI is during the first 3 postoperative days.[50,57] Why is this? Continuous ECG recording suggests that heart rate remains relatively low in the preoperative period and decreases further following induction and during surgery. Significant and substantial increases in heart rate may occur at extubation and emergence from anesthesia, and the heart rate then continues to increase during the first 12 to 24 hours postoperatively (Fig. 1). In this typical example, in a patient with unsuspected CAD, who had the risk factors of hypertension and smoking, myocardial ischemia was diagnosed on the first postoperative day when the heart rate exceeded 90 minutes^{-1}, but did not occur either preoperatively or intraoperatively. This suggests that postoperative MI in certain patients following noncardiac surgery may be prevented by the postoperative institution of anti-ischemic measures. In these previously untreated patients, it would seem reasonable to begin therapy when ischemia is diagnosed, by the introduction of heart rate reducing measures such as beta blockade and/or control of pain and anxiety.

SUMMARY

Intraoperative ischemia is common and appears to be benign when treated appropriately. However, mortality from postoperative MI remains one of the important and potentially preventable complications of anesthesia and noncardiac surgery. Major improvements in the medical and surgical therapy and outcome of CAD suggest that further reductions in postoperative cardiac morbidity are feasible. Although all perioperative myocardial ischemia is not related to recognizable changes in cardiovascular variables, the early and aggressive treatment of increased heart rate is a critical aspect of the anesthesiologist's role in prevention of perioperative cardiac events. Further ap-

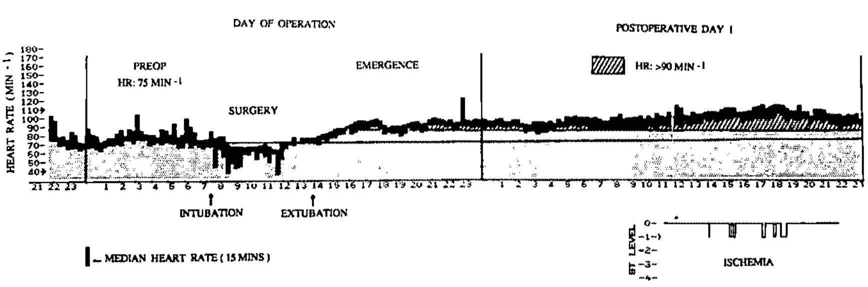

Figure 1. A 62-year-old man with unsuspected CAD underwent abdominal surgery. Preoperative heart rate was variable, but averaged 75 minute^{-1}. Heart rate decreased during surgery and enflurane-fentanyl-nitrous oxide-oxygen anesthesia. Postoperatively, the heart rate gradually increased and ischemia occurred 24 hours following extubation.

plication of new techniques in ischemia detection will provide new insights into the characteristics and efficacy of interventional therapy for perioperative myocardial ischemia and MI.

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Detection of Myocardial Ischemia and Infarction

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Among anesthetic-related deaths, cardiac causes have long been recognized as major contributors, but attention had been focused on the development of arrhythmias rather than myocardial ischemia. Only since 1976 have any specific recommendations been made to monitor patients intraoperatively for ischemia, using the electrocardiogram (ECG). [12,23] With the subsequent recognition that ischemia occurs frequently in the perioperative period and is often missed by the intermittent observation of the ECG display, improved methods of monitoring for ischemia have been developed. The most significant of these now include simultaneous display of multiple ECG leads, automated on-line ST analysis, and the new technology of transesophageal two-dimensional echocardiography. It is the intent of this article to bring the reader up to date with the theory, value, and practical use of these newer modalities.

ELECTROCARDIOGRAPHY: LEAD SYSTEMS FOR ISCHEMIA DETECTION

It is now generally accepted that an optimal and practical intraoperative lead system includes the four limb leads and one chest lead in the V_5 position as recommended by Kaplan and King in 1976.[23] It had been previously shown with exercise stress testing that 89 per cent of all post-exercise ST-segment depression was detected in lead V_5, making this the most sensitive single lead for ischemia[5] The additional ability to view the inferior leads II, III, and aVF further enhances the chance

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of detecting ischemia. More recently it has been noted by Kates et al that ischemia in the posterior wall of the heart may be detected only with an esophageal electrode.[25] A disposable esophageal stethoscope fitted with two conductive tape electrodes is now commercially available, and is considerably cheaper than the esophageal electrodes employed by cardiologists for electrophysiologic studies (Fig. 1). Thus, the anesthesiologist may position electrodes to examine all major surfaces of the heart except where surgical access limits their placement. In practice, many ECG monitors do not permit simultaneous display of two leads and may only have a three-electrode system. Thus, bipolar leads are frequently employed in monitoring, and a compromise may have to be made between monitoring for arrhythmias and monitoring for ischemia. Of the various bipolar leads described, CS_5 and CM_5 leads provide a good alternative to a V_5 lead to monitor for ischemia (Fig. 2).

ST-SEGMENT DEPRESSION AND OTHER ECG MANIFESTATIONS OF ISCHEMIA

Electrocardiographers categorize the spectrum of impaired coronary perfusion into three degrees of severity: ischemia, injury, and infarction. The effects of these on the ECG result from the delay or repolarization caused by the hypoxic myocardium. Thus, the T wave and ST segment are primarily affected. Ischemia tends to begin in the subendocardium, causing tall peaked

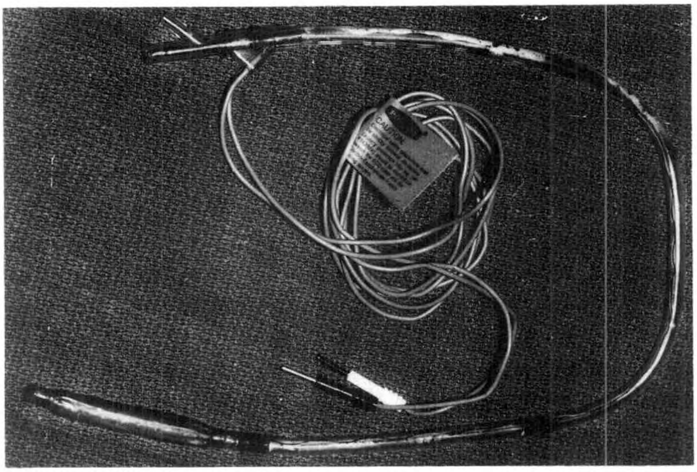

Figure 1. Cardioesophagoscope (Portex Inc.). A disposable esophageal stethoscope fitted with two (black tape) esophageal electrodes.

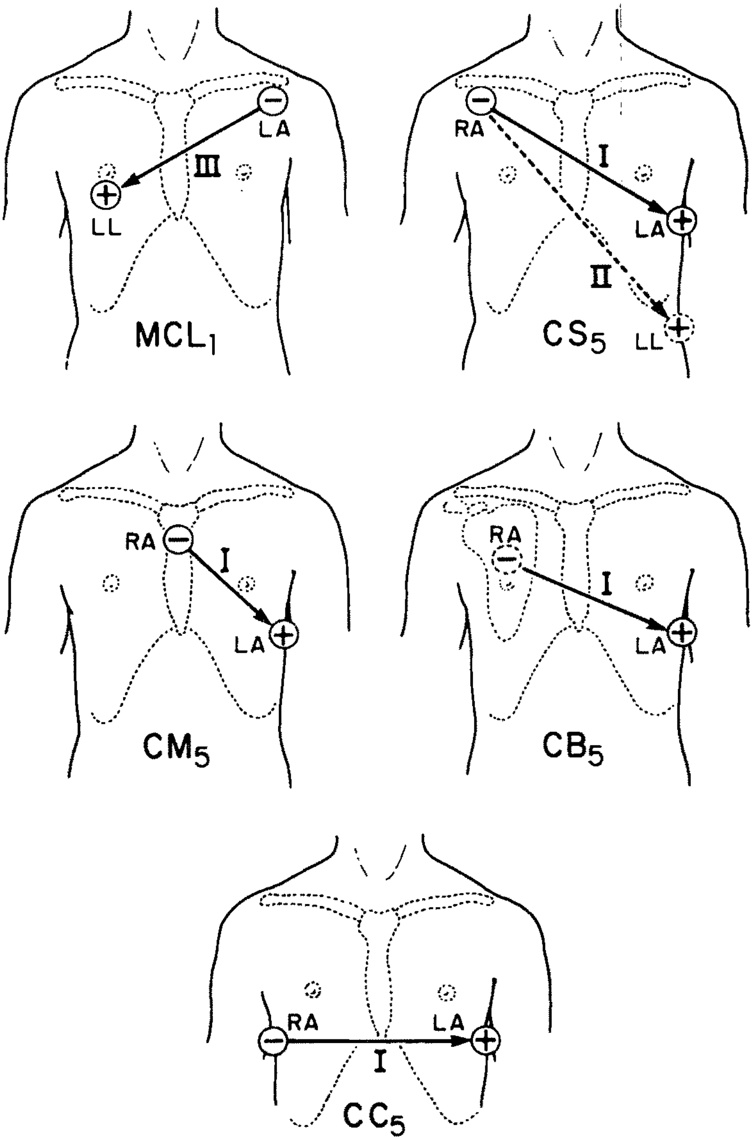

Figure 2. Modified bipolar standard limb leads. (*From* Thys DM, Kaplan JA: The ECG in Anesthesia and Critical Care. New York, Churchill Livingstone, 1987; with permission.)

T waves and ST-segment depression in the leads "facing" the ischemic region. Ischemia involving the subepicardium, generally implying more severe, transmural ischemia, alters the normal direction of repolarization and creates ST elevation with an inverted T wave (Fig. 3). Much attention has been devoted to the definition of ST-segment depression, which is the most

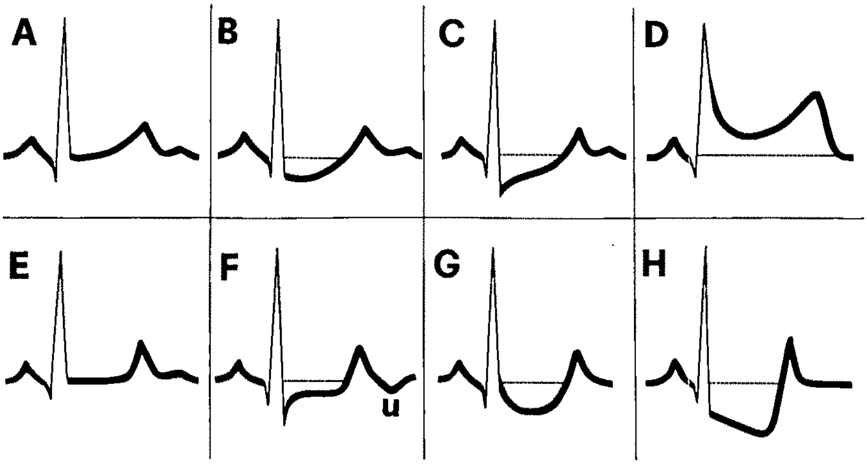

Figure 3. Diagram showing (A) normal P-QRS-T complex; (B) junctional ST-segment depression; (C) upsloping ST-segment depression; (D) ST-segment elevation and T wave amplitude increase caused by variant angina pectoris; (E) horizontality of the ST segment with a sharp-angled ST-T junction; (F) planar ST-segment depression with U wave inversion; (G) sagging ST-segment depression; (H) downsloping ST-segment depression. (*From* Schamroth L: The Electrocardiology of Coronary Artery Disease. Blackwell, Oxford, 1984; with permission.)

frequently encountered expression of ischemia in the clinical monitoring setting. Ellestad et al have defined myocardial ischemia as 1 mm or more horizontal or downsloping ST-segment depression at a point 0.06 ms after the J point.[15] The selection of a point 0.06 to 0.08 ms after the J point is very important because of the frequency of J-point depression in conditions other than ischemia. Notably, exercise causes J-point depression and upsloping ST segments that are indistinguishable from the earliest evidence of ischemia. During exercise-induced ischemia, the ST segments progress from upsloping to horizontal and then downsloping; thus, time may distinguish true ischemia. The slope of the ST segment has also been regarded as a critical factor, with a slope of more than 40 per cent at a paper speed of 25 mm per second being regarded as "probably normal."[6] Upsloping ST segments may still be associated with significant coronary disease, however. In patients undergoing stress testing, Stuart and Ellestad found that there was the same incidence of coronary disease in those patients with upsloping ST segments as in those with horizontal ST-segment depression, provided that there was also 2 mm depression 0.08 ms after the J point.[39] Downsloping ST segments, however, carry a worse prognosis than either horizontal or upsloping ones.[18]

Other factors, such as left ventricular hypertrophy, administration of digoxin or quinidine, hypokalemia and intraventricular conduction delay also affect the ST segment, confounding the diagnosis of ischemia. Electronic filtering is also capable of distorting the ST segment, leading to misdiagnosis. Whereas 12-lead ECGs are taken with some care, instructing the patient to lie still without speaking, bedside monitors are designed to filter out signals produced by movement of the patient and by other electrical equipment attached to the patient. Thus, the monitor may distort incoming signals with a frequency below 0.5 Hz, preserving a stable baseline and readable QRS complex at the expense of interfering with the reproduction of the ST segment. Some monitors permit the operator to select a "diagnostic mode" of operation, in which the low-frequency cut-off is 0.05 Hz, permitting more faithful reproduction of the ST segment.[4]

AUTOMATED ST-SEGMENT ANALYSIS

Unfortunately, it has been shown many times that ST-segment depression displayed on a monitor goes unnoticed by the anesthesiologist, whose attention is necessarily directed to the multiple tasks associated with anesthetic management.[10,34] Transient, small changes in ST-segment depression are difficult to detect unless hard copy tracings are retained and compared. Thus, in association with technological developments that have improved the accuracy of the ST-segment display, interest has developed in automated ST-segment analysis and trend recording. This on-line capability appears to enhance the detection of ischemia and provides continuous feedback after therapeutic interventions.

Automated ST-analysis systems incorporate a computer algorithm with which the QRS complex can be correctly identified; for each complex a baseline isoelectric and an ST-segment point can then be defined and compared. Several manufacturers are now developing ST-analysis software for use with their standard bedside monitor. The currently available Marquette system (Marquette Electronics Inc, Milwaukee, WI) examines three leads: I, II, and V_5. An isoelectric baseline point is selected 16 ms prior to the onset of the QRS complex and compared with an ST-segment point 40 ms after the offset of the QRS. However, these points are manually adjustable, which can be useful with a widened QRS complex (Fig. 4). The absolute value of ST deviation (millimeter elevation or depression) for each of the three leads is added together without regard for

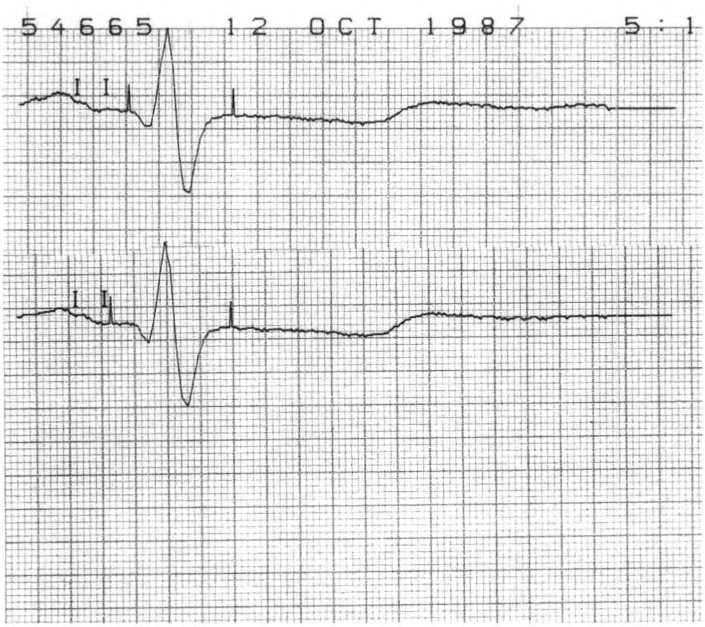

Figure 4. Automated ST-segment analysis and display. (Marquette system). (Top) The default isoelectric and ST segment points are shown. (Bottom) The isoelectric point has been manually shifted to select an earlier point prior to the QRS complex.

the direction of deviation to provide an "ST-deviation plot" for 28 minutes of recording time. An upward trend indicates more ST deviation and thus more ischemia. The QRS templates for the three leads are updated every 32 beats. Figure 5 illustrates the QRS templates and ST-deviation plot recorded in a patient who became ischemic during cannulation prior to cardiopulmonary bypass. When the plot was printed, ischemia was resolving, as shown by the sharp decline seen at the far right end of the deviation plot; at the left side of the figure the QRS tem-

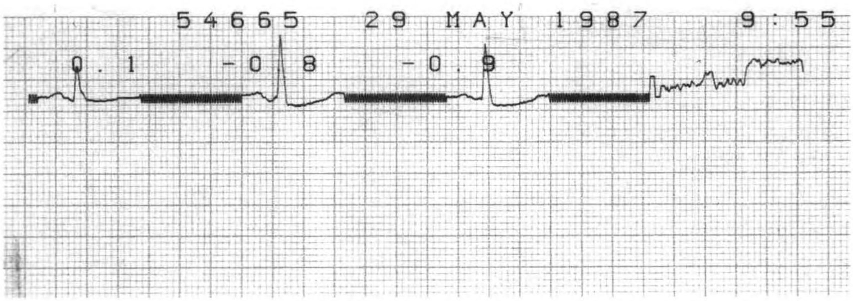

Figure 5. An "ST deviation plot" (Marquette system). ST deviation for the preceding 28 minutes is shown. The rising line shown at right indicates the development of ischemia (ST depression in leads II and V_5), which improves markedly at the very end of the recorded time (see text).

plates for leads I, II, and V show 0.1 mm ST elevation, 0.8 mm ST depression, and 0.9 mm ST depression, respectively.

An early version of this analysis system was used by Kotter et al to study the incidence of ischemic events and their relationship to hemodynamics during the pre-bypass phase of open heart surgery.[27] Among their findings, the authors noted that the incidence of ischemia decreased significantly from 17 per cent to 6 per cent after the first 6 months of the study. They felt that this was due to the acceptance of the ST-analysis system, resulting in an increased awareness of small ST-segment changes and prompt interventions to correct them.

Aside from bedside monitors, cardiologists have been interested in developing automated ST-segment analysis for portable "Holter" monitors, in order to assess the amount of ischemia occurring during daily activities. Formerly, the AM recording systems used in portable ECG monitors suffered from a limited ability to record the low frequencies that include the ST segment. Thus, ambulatory monitors were somewhat discredited for the purpose of detecting ischemia. However, technological improvements have taken place and studies have now validated some portable monitors for the detection of ST-segment changes. Automated, real-time analysis has become essential to deal with the vast amount of information generated by long-term ECG recording and to develop an interactive capability with which the patient can be alerted to the presence of ST-segment depression; he can then record his activity and symptoms or take some prescribed medication. A number of commercially available portable monitors have now been developed to serve these purposes, using AM or FM tape recorders or solid state memory: some offer an interactive capability; some use one bipolar lead and others allow simultaneous recording of two.

Such monitors are now being used in hospitalized patients who are at risk for developing ischemia and infarction. We have studied patients during the perioperative period with a portable solid-state monitor (Monitor One, QMed, Clark, NJ) that performs real-time ST analysis and retains significant events in memory for later retrieval in hard copy form. In addition, it can be programmed to alarm for selected events, allowing for immediate treatment, and the memory can be accessed at any time during monitoring to ascertain the number and duration of significant events recorded. An ischemic event is recorded when ST-segment depression of at least 1 mm at a point 60 ms after the J point persists for a minimum of 40 or 60 seconds (manually selected). Five seconds of the ischemic time is retained in memory to provide a representative QRS tracing later. In addition, histograms showing trends of heart rate, ST-segment level, and ventricular ectopy are presented in the final report.

We have found a 37 per cent incidence of perioperative ischemia in 24 patients undergoing peripheral vascular surgery who were monitored for a mean time of 74.5 hours.[9] ST-segment depression was accompanied by pain in only one patient, who was considered clinically to have unstable angina and also had several episodes of painless ST-depression. In an attempt to reduce his ischemic time as much as possible, the monitor's audible alarm was programmed to sound for ST-segment depression so that the intensive care unit staff would be alerted and could adjust therapy as necessary. Of the eight patients who exhibited episodes of ST-segment depression, three had unfavorable outcomes: two developed congestive heart failure and died and a third suffered a myocardial infarction within a month of hospital discharge. None of the 16 other patients studied had significant cardiac events. Thus, in this small group of surgical patients, ST-segment depression was associated with significant morbidity and mortality. Histograms of heart rate and ST level during the period of monitoring have revealed that ST-segment depression is associated with tachycardia in many patients, but this is not an invariable feature. The effect of beta-blockade in a patient with rate-related ischemia is shown in Figure 6. This patient had a strong family history of coronary artery disease and evidence of a previous myocardial infarction on his 12-lead ECG. However, he had no

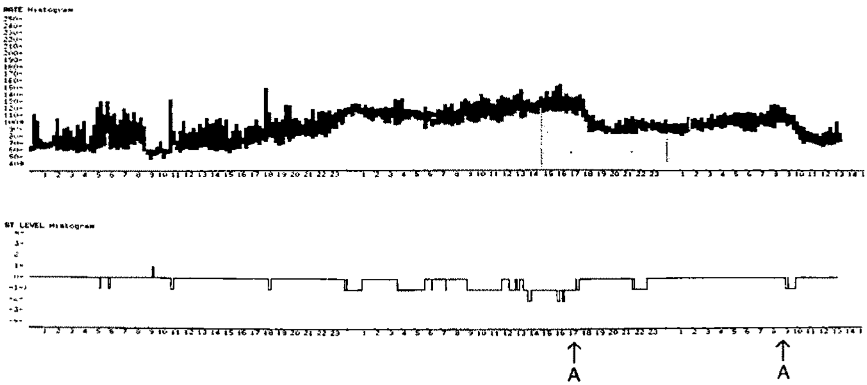

Figure 6. The heart rate and ST-level histograms are shown for a patient who experienced several episodes of silent ischemia following surgery. The effect of atenolol 50 mg given at A is shown.

clinical history for a myocardial infarction or anginal pain and refused cardiac catheterization.

The significance of ST-segment depression and the value of using automated ST analysis to detect it perioperatively has been suggested by our observations of a patient who sustained a postoperative myocardial infarction in the intensive care unit.[8] As part of a clinical research protocol this patient was monitored simultaneously with the standard bedside monitor (no ST analysis capability) and with a portable (QMed) monitor. On day 3 following surgery he sustained a large anterior wall infarction complicated by ventricular fibrillation requiring repeated cardioversion. Prior to this event the patient made no complaints of chest pain but had frequent premature ventricular beats and was persistently tachycardic and hypertensive. No ST-segment depression was observed on the standard monitor by the intensive care unit staff; however, review of the portable monitor report showed that four ischemic events had occurred, all within 5 hours of the infarction (Fig. 7). In addition, the histograms revealed a trend of increasing ventricular ectopy and persistent tachycardia during the 40 hours of recording (Fig. 8). Activation of the audible alarm could have alerted the intensive care unit staff to the development of ST-segment depression and prompted some additional therapeutic intervention.

CHARACTERISTICS AND SIGNIFICANCE OF SILENT ISCHEMIA

It has recently come to light that 70 to 85 per cent of ischemic episodes are unaccompanied by angina, thus "silent ischemia" is a prominent feature of coronary artery disease.[13,35] It can no longer be assumed that an awake patient will develop angina with each episode of ischemia and thus provide his own warning system. Symptoms of coronary disease are now seen to represent only the tip of the iceberg and the new concept of "total ischemic burden" has evolved as a more meaningful index of myocardial oxygen balance in a given perior of time. Long-term monitoring with automated ST analysis is now providing new information about the frequency and significance of ischemic events in populations at risk.

Deanfield et al have shown that 60 to 80 per cent of patients with chronic stable angina have daily episodes of ischemia, or five to ten episodes per week[14] with a median duration of 17 minutes (range 1 to 90). Painful episodes tend to last longer

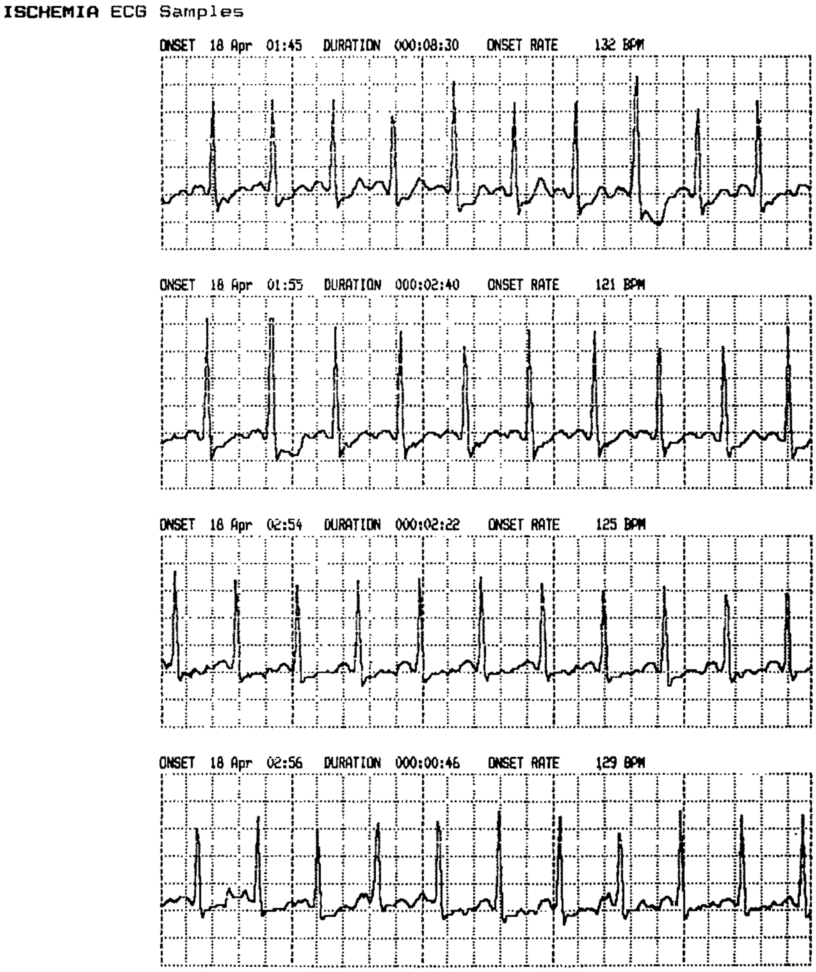
ISCHEMIA ECG Samples
ONSET 18 Apr 01:45 DURATION 000:08:30 ONSET RATE 132 BPM
ONSET 18 Apr 01:55 DURATION 000:02:40 ONSET RATE 121 BPM
ONSET 18 Apr 02:54 DURATION 000:02:22 ONSET RATE 125 BPM
ONSET 18 Apr 02:56 DURATION 000:00:46 ONSET RATE 129 BPM

Figure 7. Five-second ECG traces recorded by a QMED ambulatory monitor during ischemic episodes (1 mm ST-segment depression), occurring shortly before an extensive anterior wall myocardial infarction. (*From* Clements FM, McCann RL, Levin RI: Continuous ST-segment analysis for the detection of perioperative myocardial ischemia. Crit Care Med, July 1988, pp 710–711; with permission.)

than painless ones: 21 ± 7 minutes versus 16 ± 5 minutes,[28] but there appears to be no correlation between the degree of ST depression and the occurrence of pain. Furthermore, 70 per cent of episodes occur at rest or with minimal physical activity and may be more related to mental activity. In the same vein, it has been observed that the heart rate at onset of silent ischemia in daily life is significantly lower than the heart rate at onset of ischemia during exercise stress testing in the same patients. Thus, it is clear that factors other than increased myocardial

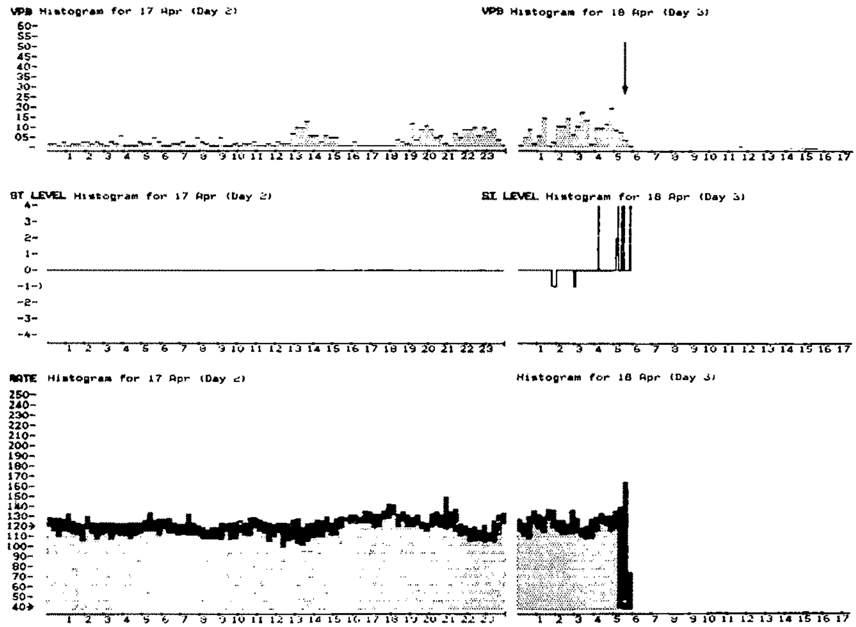

Figure 8. Trends of premature ventricular beats (VPB histogram), ST level (ST-level histogram), and heart rate (HR histogram) over 40 hours preceding an anterior wall myocardial infarction (QMED report). Hard copy traces of the recorded ischemic episodes recorded prior to the MI are presented in Fig. 7. The apparent ST elevation noted in this report could not be confirmed in hard copy form with the monitor used, and may have been artifactual. The patient suffered a cardiac arrest at 05.30 and required electrical defibrillation several times before sinus rhythm was restored. (*From* Clements FM, McCann RL, Levin RI: Continuous ST-segment analysis for the detection of perioperative myocardial ischemia. Crit Care Med, July 1988, pp 710–711; with permission.)

oxygen demand are playing a significant role in the generation of ischemia. There is also a diurnal variation in the frequency of ischemic episodes, with more occurring between the hours of 6 and 10 AM, as is seen with myocardial infarctions and sudden death.

In patients who have coronary disease but no history of angina or myocardial infarction, the prevalence of silent ischemia is 2.5 to 10 per cent.[16,28] On the other hand, patients with clinical unstable angina, receiving maximal medical therapy in a coronary care unit, have a 50 per cent incidence of silent ischemia.[19] In this population the presence and duration of silent ischemia has also proved to be a better predictor of poor outcome than the presence of continued chest pain with greater than 60 minutes of ischemia per 24 hours being associated with a less favorable outcome.

Unfortunately, although currently available monitors appear to be suitable for the detection of ischemia, ST segments cannot be reliably interpreted in the presence of digoxin or quinidine therapy or left ventricular hypertrophy. Further work may allow ischemia-related ST-segment depression to be defined for the many patients who fall into these categories.

DETECTION OF MYOCARDIAL ISCHEMIA AND INFARCTION BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Tennant and Wiggers reported in 1935 that ligation of a coronary artery produced an almost immediate failure of contraction in the ischemic area of the myocardium. They observed in open-chest dogs that the affected myocardium initially appeared to contract poorly, became immobile, and subsequently appeared to bulge outward during systole.[40] In recent years, two-dimensional echocardiography has become a practical method for evaluating the regional wall motion abnormalities associated with ischemia and infarction. The intraoperative use of echocardiography as a monitoring modality has evolved as a result of the esophageal transducer, which can be positioned in the esophagus for the duration of monitoring (Figs. 9 and 10). Consequently, anesthesiologists are now becoming acquainted

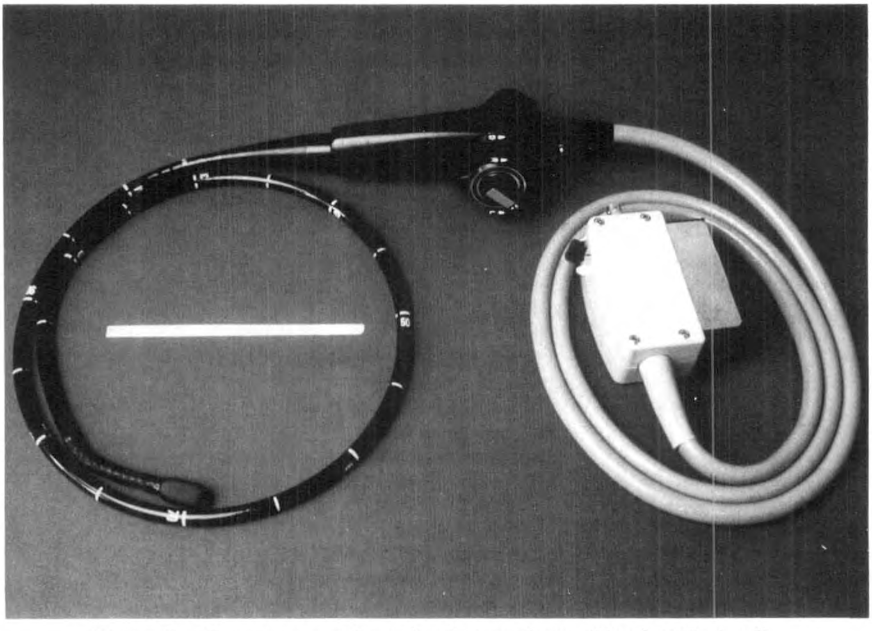

Figure 9. Prototype esophageal echotransducer (Hewlett-Packard).

with the spectrum of regional wall motion abnormalities that characterize ischemia and infarction.

"Wall motion abnormality" is a nonspecific term applied to an area of myocardium that is moving abnormally. Wall motion abnormalities can occur during both systole and diastole, but systolic wall motion abnormalities have been more extensively investigated. As the ventricle contracts, the myocardium thickens, the ventricular cavity becomes smaller, and the stroke volume is expelled into the aorta. Thus, systolic wall motion is described by the movement of the endocardium toward the center of the left ventricular cavity and by the increase in myocardial wall thickness. Unlike ventricular angiography, echocardiography defines both endocardium and epicardium, allowing a more accurate definition of wall motion[7] (Figs. 11A and B).

In monitoring regional wall motion, the short-axis image of the left ventricle is used (Figs. 11 and 12). This cross-sectional view images segments of myocardium supplied by all three coronary arteries and is the single image most likely to reveal ischemia and infarction.[20] The inferior wall, situated closest to the transducer, is supplied by the right coronary artery, the anterior wall and anterior two thirds of the septum is supplied by the left anterior descending coronary and the lateral and posterolateral regions represent the circumflex coronary. The

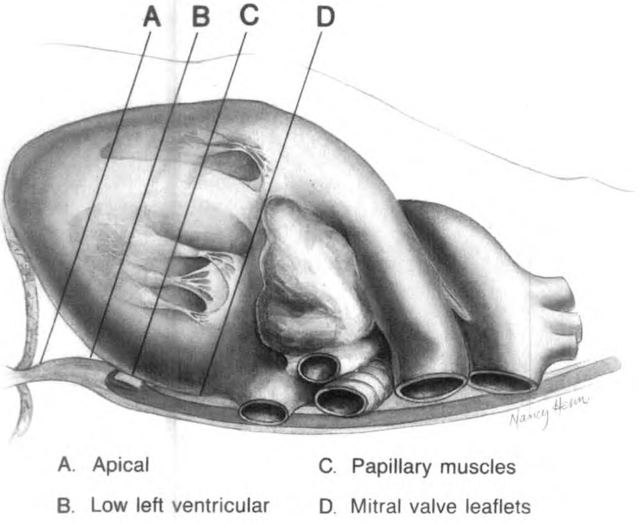

Figure 10. Transesophageal echotransducer in situ to record various short-axis images. The approximately parallel alignment of the esophagus with the long axis of the heart allows short-axis images to be recorded at several levels as indicated.

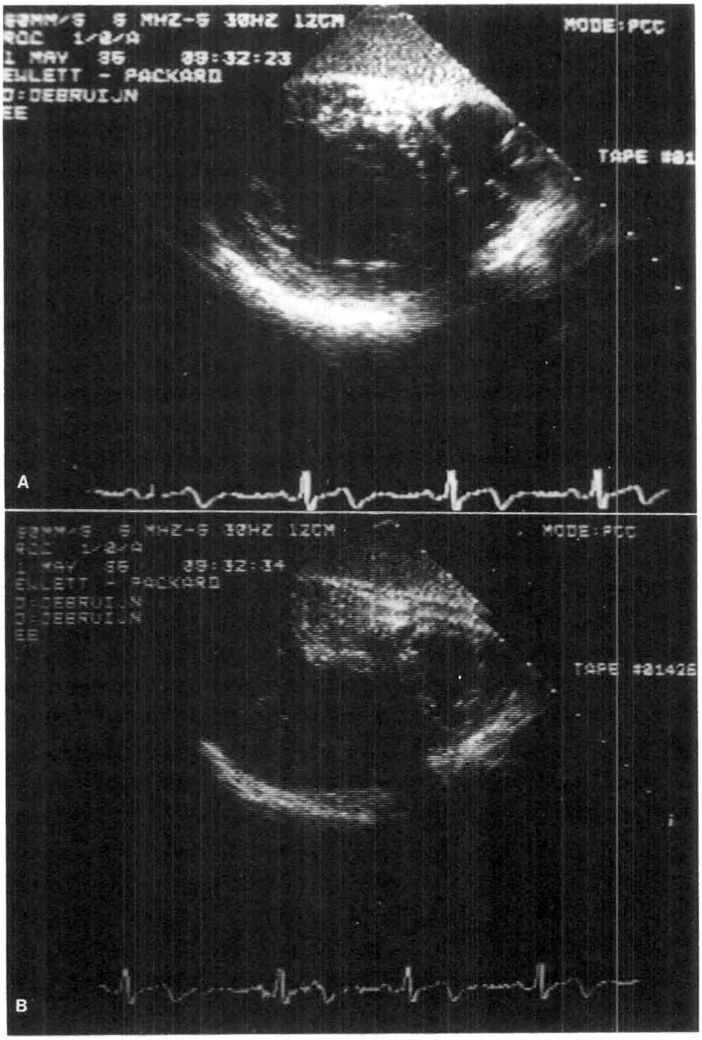

Figure 11. Left ventricular short-axis images at the papillary muscle level. (A) Diastole. (B) Systole.

anesthesiologist must develop the habit of examining each segment of the myocardium in turn during systole, evaluating the inward motion of the endocardial surface and the degree of systolic wall thickening. The ventricular circumference may be conveniently divided into four or five segments for descriptive purposes, for example, anterior, lateral, inferior, and septal (see Fig. 12). Images recorded on videotape during the course of surgery can be recalled to the screen for comparison with later images and the effects of therapeutic interventions can be assessed.

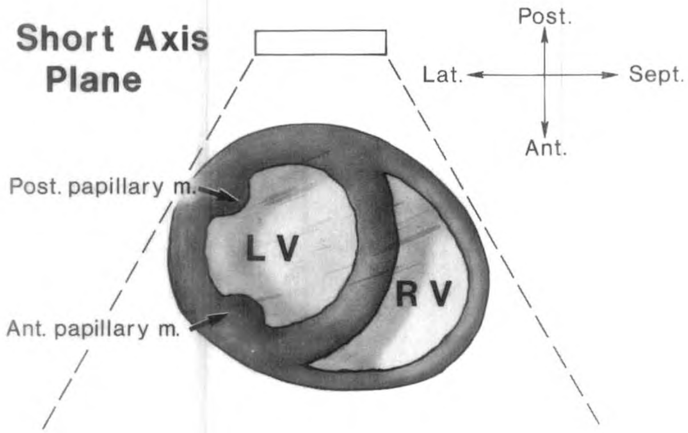

Figure 12. Diagram of a short-axis view of the heart. Both papillary muscles are indicated. The posterior left ventricular wall is closest to the transducer.

Several terms are used to describe abnormal wall motion (Table 1): hypokinesia (mild or severe) describes reduced contraction of the myocardium; akinesia describes nonmoving myocardium; and dyskinesia refers to bulging of the myocardium during systole. In addition, the contraction may be described simply as asynergic, meaning that it is abnormal or asynchronous, implying that contraction is not occurring simultaneously around the ventricle.

DEVELOPMENT OF REGIONAL WALL MOTION ABNORMALITIES

The occurrence of wall motion abnormalities immediately following the onset of myocardial ischemia is a result of tissue hypoxia. Without oxygen the production of adenosine triphosphate (ATP) fails, the regulatory function of ATP is impaired, regional acidosis develops, and the net effect is an impaired

Table 1. *Terms Used to Describe Myocardial Contraction*

Normal	Endocardium moves inward Myocardium thickens uniformly
Hypokinesia	Inward endocardial motion and wall thickening are reduced
Akinesia	Endocardium does not move toward the center of the LV and myocardium does not thicken
Dyskinesia	Endocardium moves outward (paradoxically) in systole; myocardium does not thicken

function of the contractile elements. If the hypoxia is of limited duration, these effects are reversible, but after 5 to 20 minutes of ischemia histologic changes occur; with prolonged ischemia irreversible changes take place, involving most cells in an ischemic area after 60 minutes.

In experimental animals, complete coronary occlusion is followed by hypokinesia within 10 to 15 seconds. This progresses to akinesia and dyskinesia after 30 to 60 seconds.[3,26,37] Similar observations have recently been made in patients undergoing coronary balloon angioplasty.[1] With controlled, graded coronary stenosis, this relationship of hypokinesia, akinesia, and dyskinesia persists: as a coronary artery is progressively occluded, the initial regional wall motion abnormality is hypokinesia, which appears at approximately 50 per cent reduction in coronary flow and progresses to dyskinesia at 90 to 95 per cent reduction in flow (Fig. 13). Brief coronary occlusions are followed by complete functional recovery within 45 seconds[31] and may even result in a transient hypercontractility due to reactive hyperemia and catecholamine release. An isolated regional wall motion abnormality, however, may also produce some deleterious effects on the adjacent myocardium.

Experimental work has shown that with acute coronary occlusion there is depression of myocardial function beyond the

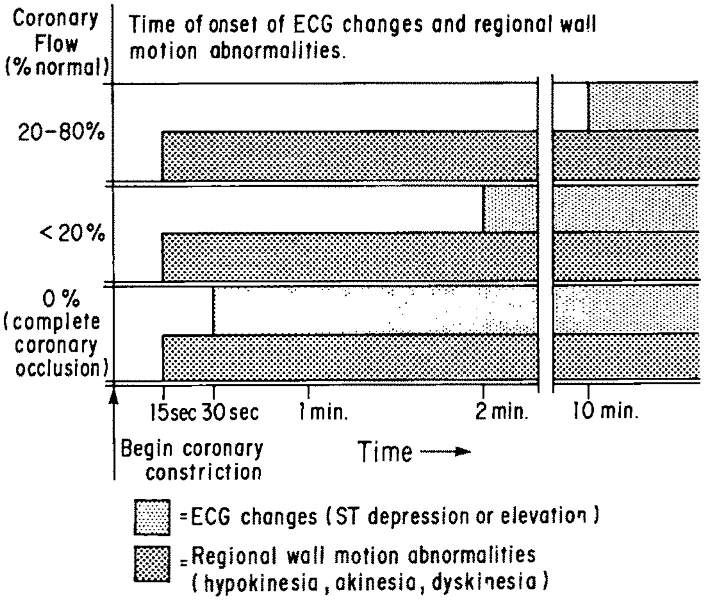

Figure 13. Temporal relationship between acute coronary constriction and onset of ECG changes and regional wall motion abnormalities.

infarct zone, the magnitude of which is inversely related to the distance from the infarct. This decrease in function beyond the infarct zone occurs without local ST-segment changes and without alterations in local perfusion.[22,33,44] This effect of regional ischemia on neighboring nonischemic zones is probably in part attributable to a "tethering" effect (Fig. 14); the noncontracting fibers appear to impair the function of the adjacent normal fibers with which they are interwoven. Experimentally, wall thickening has been shown to delineate the extent of an infarct more precisely than endocardial motion.[29,30] Lieberman et al also observed that an infarct involving less than 20 per cent of the wall thickness showed reduced wall thickening, whereas more than 20 per cent involvement caused wall thinning.

REPERFUSION AND REGIONAL WALL MOTION

Although the onset of a regional wall motion abnormality occurs almost simultaneously with ischemia, the restoration of normal wall motion may lag behind the restoration of normal myocardial perfusion to a variable degree. Heyndrickx et al have shown that a 5-minute coronary occlusion resulted in wall motion abnormalities that persisted for 3 hours, while a 15-minute occlusion resulted in contraction abnormalities lasting for more than 6 hours. This phenomenon is known as "stunned myocardium" and makes it very difficult to assess, by echocardiography, the extent of a myocardial infarction following a coronary occlusion.[21] Wyatt and Meerbaum showed this in dogs in which a 3-hour coronary occlusion was followed by 45 hours of reperfusion.[45] The extent of regional wall motion abnormality as determined by two-dimensional echocardiography was compared with the extent of the infarction by nitroblue tetrazolium

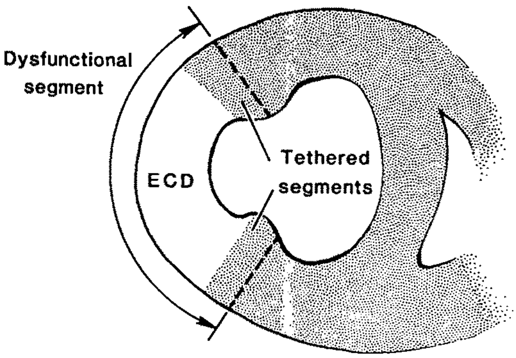

Figure 14. Diagram of a short-axis view of the left ventricle. Contrast medium injected into the coronary arteries enhances myocardium (shaded area). ECD = echo contrast defect, which identifies nonperfused ischemic myocardium. The dysfunction extends beyond the true ischemic area indicated by the ECD because of "tethering" of the infarct zone to the adjacent myocardium.

staining. A lack of correlation was observed during the reperfusion phase with myocardial edema, but the correlation improved as myocardial edema and hyperemia resolved. Patients undergoing coronary artery angioplasty for acute myocardial infarction and patients undergoing cardiac surgery may also show reperfusion wall motion abnormalities. Estimates of viable and nonviable myocardium made on the basis of echocardiographic images cannot be reliable in such patients. The observed dysfunction is real, however, and may sometimes be seen to improve with inotropic support.

RELATIVE SENSITIVITY OF THE ECG AND TWO-DIMENSIONAL ECHOCARDIOGRAPHY FOR THE DETECTION OF ISCHEMIA

Much work has been done to compare the relative sensitivity of the ECG and regional wall motion as markers for coronary insufficiency. Although the surface ECG shows ST-segment elevation as early as 30 to 60 seconds after total coronary occlusion, of more interest in the clinical setting is the occurrence of myocardial ischemia, which is much more common. Waters et al found that hypokinesia of the affected myocardium appeared first with approximately 50 per cent reduction in coronary flow, while ECG changes did not occur before there was a reduction in flow of approximately 75 per cent.[42] Comparison of changes in contractile function and ECG changes in the epicardium and the endocardium further reveal that contraction abnormalities appear first in the subendocardium and these precede ST-segment changes from endocardial leads, which themselves appear long before surface lead ECG changes. Smith et al compared surface electrocardiography and transesophageal two-dimensional echocardiography for detection of ischemia in 50 anesthetized patients with known coronary artery disease.[38] Of the 50 patients, 24 developed new segmental wall motion abnormalities intraoperatively, but only six developed ST-segment changes. ST-segment changes were always accompanied by wall motion abnormalities that develop before or simultaneously. Of the three patients who developed perioperative myocardial infarctions, only one had intraoperative ST-segment changes, whereas all had persistent new wall motion abnormalities. This clinical study corroborates the animal studies that suggest that the sensitivity and specificity of regional wall motion abnormalities for the detection of ischemia are clearly superior to the electrocardiogram.

DETECTION OF MYOCARDIAL ISCHEMIA BY MEASUREMENT OF PULMONARY ARTERIAL PRESSURES

It has long been recognized that the development of angina may be associated with a rise in the left ventricular end-diastolic pressure or the pulmonary capillary wedge pressure. For this reason there has been interest in using a pulmonary artery catheter as an additional way of detecting ischemia. Kaplan and Wells[24] investigated the use of pulmonary capillary wedge pressure as an aid in the early diagnosis of myocardial ischemia in anesthetized patients. Forty patients with progressive angina pectoris undergoing elective myocardial revascularization were studied. Ischemia was defined by one of the following conditions: ST-segment depression greater than 1 mm; a wedge pressure tracing with an abnormal AC wave greater than 15 mm Hg; or a V wave greater than 20 mm Hg. Forty-five per cent[18] of the patients developed one or more of these conditions. Three patients developed ST-segment depression only; five patients developed ST-segment depression and an abnormal wedge pressure tracing; and ten patients demonstrated only abnormal wedge pressure tracings. Similarly, Kotter et al[27] found that six of ten patients with ST-segment changes showed an increase in pulmonary artery diastolic pressure exceeding 15 mm Hg but in four patients there was no change at all in pulmonary artery pressure.

The abnormal wedge pressure tracings seen during ischemia were associated with significant elevations of the mean wedge pressure, central venous pressure, and triple product (SBP × HR × PCWP) in Kaplan's study. The authors concluded that measurement of pulmonary capillary wedge pressures can be helpful in the early diagnosis of a subendocardial ischemia, because a significant number of patients develop myocardial ischemia that is not immediately identifiable on the electrocardiogram. However, the sensitivity and specificity of pulmonary capillary wedge pressure as an indicator of myocardial ischemia have not been well established, and it is not clear how many false positives and false negatives occur. An additional disadvantage of the pulmonary artery catheter is its invasive character. Pulmonary artery perforation, probably the most catastrophic complication associated with pulmonary artery catheterization, occurs in approximately 1 in 1,500 patients.[2] Other less disastrous complications occur not infrequently and the advantage of the use of a pulmonary artery catheter has to be carefully weighed against the possible complications.

The mechanism by which the wedge pressure and the left ventricular end-diastolic pressure are elevated with ischemia has been attributed to changes in the systolic performance of the heart and to changes in its diastolic pressure-volume relationship. Because ischemia impairs the metabolism of the heart, the active process of relaxation is also impaired, resulting in an apparent increased stiffness of the myocardium. When this localized process has sufficient effect, the diastolic pressure-volume relationship may be altered and the end-diastolic pressure may rise. Weisfeldt's[43] work has supported the idea of incomplete relaxation occurring during and immediately following ischemia. However, Palacios et al[32] have concluded that the mechanism is primarily that of reduced systolic performance of the heart rather than an alteration of the pressure-volume relationship.

SIGNIFICANCE OF INTRAOPERATIVE ISCHEMIA

In patients with documented coronary artery disease, the reported incidence of intraoperative myocardial ischemia has ranged from 26 to 67 per cent, using the electrocardiogram (see also articles by Lake and McIntyre and Hart in this issue). Since patients with coronary disease may have daily episodes of ischemia during their usual activities, it has not been clear how much significance should be specifically attached to intraoperative ischemic episodes. In 1986, Slogoff and Keats reported that ischemia occurred in 36.9 per cent of 1,023 patients undergoing coronary artery bypass grafting.[36] In this series, perioperative myocardial infarction was three times more frequent in patients with ischemia as in those without: 6.9 versus 2.5 per cent. Recently, Kotter et al have reported an 11.9 per cent incidence of ischemia by ECG during the pre-bypass phase of coronary surgery.[27] Fewer patients undergoing a first-time procedure had ischemia (8.1 per cent) than patients having a "redo" procedure (23.5 per cent); patients having a combined valve replacement coronary artery bypass graft had the most ischemia (35.3 per cent). The authors found that the incidence of ischemia was the same whether or not the patients were taking antianginal therapy. In patients with coronary disease undergoing noncardiac surgery, Coriat et al reported a 42 per cent incidence of ischemia.[11] Intravenous nitroglycerin has not been uniformly effective in reducing ischemia in surgical patients.[10,17,41]

Perioperative myocardial ischemia remains a frequent occurrence in patients with coronary disease and carries increased risks that may be modified by appropriate therapy. Automated ST analysis is beginning to reveal information about silent ischemia that promises to be as important to the anesthesiologist in the management of these patients as it is to the cardiologist managing the chronic sufferer of coronary artery disease.

PRACTICAL ASPECTS OF ISCHEMIA MONITORING

Recent advances in automated ST-segment analysis appear to enhance the value of ECG monitoring considerably, with little additional cost. As always, the placement of the leads remains the most important aspect of ischemia detection using the ECG. It appears that the extension of automated ST analysis into the longer term perioperative period will reveal other periods of risk that could be more effectively addressed to reduce overall perioperative cardiac morbidity. The introduction of transesophageal echocardiography into the practice of anesthesia unquestionably provides a sensitive monitor of ischemia, with the additional benefit of information about global function and dimensions of the heart, valvular competence, and intracardiac shunting. Furthermore, the clinical, qualitative interpretation of regional wall motion appears to be relatively easily learned and applied.[7] On-line quantitative measurements are not yet feasible, however, and the equipment is expensive. The ease of performing transesophageal echocardiography in anesthetized patients and the relatively noninvasive nature of the technique make it an attractive monitor for patients at high risk for ischemia, especially for those in whom a pulmonary artery catheter would not otherwise be required. Transesophageal echocardiography has been used safely in several thousand awake and anesthetized patients. No mechanical or thermal injuries to the esophagus have been reported, even in fully heparinized patients who have been monitored for several hours. A single report of vocal cord injury has occurred, however, in a patient undergoing a sitting craniotomy with maximal neck flexion (Cucchiara, personal communication). The injury was attributed to the compression of the vocal cord between an armored endotracheal tube and the flexible, but noncompressible, echoscope in this nonphysiologic position. Certainly, the safety of transesophageal echocardiography compares very favorably with that of the pulmonary artery catheter.

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Myocardial Protection: Role of Vasoactive Drugs

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Prevention and treatment of perioperative myocardial ischemia has advanced remarkably in recent years. Detection of intraoperative ischemia is now far more sensitive, as invasive and noninvasive cardiac monitoring has become more sophisticated. A wide range of anesthetic agents allows individualization of anesthetic management tailored to each cardiac patient. In addition, a wide array of vasoactive agents is available for perioperative intravenous administration, enabling hemodynamic and cardiac parameters to be adjusted during the course of surgical interventions.

Vasoactive agents can be broadly classified as dilators and constrictors. Vasodilating agents have been successfully used to minimize the area of myocardial infarction in experimental conditions, as well as decrease angina and ST-segment elevation in humans.[27,28,31,43,74,107] The vasoconstrictors employed in ischemic heart disease consist mainly of alpha-adrenoreceptor agonists, and these agents have been used concomitantly with vasodilators to optimize coronary perfusion pressure and vascular resistance. These alpha agonists also may have a role in the management of right ventricular failure. Inotropic agents, which have alpha- or alpha- and beta-agonist activities, can improve or worsen ischemia.

NITROGLYCERIN

Oral nitroglycerin has been in use as an antianginal drug for over a century. Previously available only in oral form, trans-

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dermal and intravenous nitroglycerin have enabled this drug to be used perioperatively. Intravenous use requires a special, nonadsorbing plastic administration set to ensure reliable drug delivery, while transdermal preparations only need to be applied to a normally perfused area of skin. Transdermal application has become simpler and more reliable with the advent of a gel-matrix delivery system, thus obviating the need for accurate measurement and application of nitrate-containing paste.

Although nitroglycerin has long been known as an effective agent in angina pectoris, its mechanism of action in alleviation of myocardial ischemia is still uncertain.[26,66] Nitroglycerin has been extensively researched in the past 15 years in both animal models of acute infarction and in patients with acute myocardial infarction. Oral and intravenous preparations, as well as intracoronary versus systemic intravenous administration, have been used and compared for efficacy in the relief or elimination of myocardial ischemia.

The effects of nitroglycerin differ when administered intravenously or orally as opposed to injected directly into the affected coronary artery. Ganz and Marcus, in an elegant series of experiments, found that intravenous nitroglycerin was effective in reducing ischemia, while intracoronary nitroglycerin had little effect.[34] They suggested that the systemic effects of the drug were more important than its direct effects on ischemic myocardium. Subsequent studies of intravenous nitroglycerin have shown that there is a difference in response to the drug, depending on the level of left ventricular function. Patients with good left ventricular function benefited from nitroglycerin, while those with poor left ventricular function or heart failure had worsening of their ischemia.[7] Further investigations suggested that coronary perfusion pressure was critical in the response of patients with marked left ventricular impairment to nitroglycerin: If perfusion pressure was kept constant with concomitant infusion of methoxamine, nitroglycerin had a beneficial effect in reducing ST-segment depression, while nitroglycerin alone caused a significant drop in perfusion pressure and worsening of ischemia.[75]

Other studies have concentrated on the coronary vasodilating properties of nitroglycerin and suggested that nitroglycerin's alleviation of ischemia is due mainly to this vasodilation.[8,22,33] Nitroglycerin has been shown to decrease coronary collateral vascular resistance in a model of chronic coronary occlusion.[16] This model allowed significant collateralization of the infarcted areas. When the perfusion pressure of the normal artery supplying the collateral vessels was reduced, myocardial ischemia in the collateralized area ensued. Nitroglycerin reduced this ischemia (measured by ST-segment depression) and decreased the pressure gradient between the "donor" and the collateralized vessel, which was interpreted as dilation of the coronary collaterals and alleviation of ischemia. In an acute model of coronary occlusion, intravenous nitroglycerin resulted in improved regional myocardial function in the border zone area of infarction.[108]

Thus, nitroglycerin is thought to improve myocardial ischemia by four mechanisms (Fig. 1). By reduction of preload, and a slight reduction in afterload when given intravenously, nitroglycerin reduces systolic wall tension and decreases myocardial oxygen demand. The reduction in preload may also increase subendocardial collateral perfusion. The dilation of coronary collateral vessels may improve myocardial oxygen supply, thus also alleviating ischemia. Additionally, coronary spasm, which may incite or exacerbate ischemia, is reversed by nitrates.[66]

With evidence of the efficacy of nitroglycerin in relieving myocardial ischemia, many patients are currently treated perioperatively with nitroglycerin. Intraoperative intravenous nitroglycerin has been shown to effectively reduce ST-segment abnormalities, presumably by decreasing determinants of myocardial oxygen demand during acute hypertensive

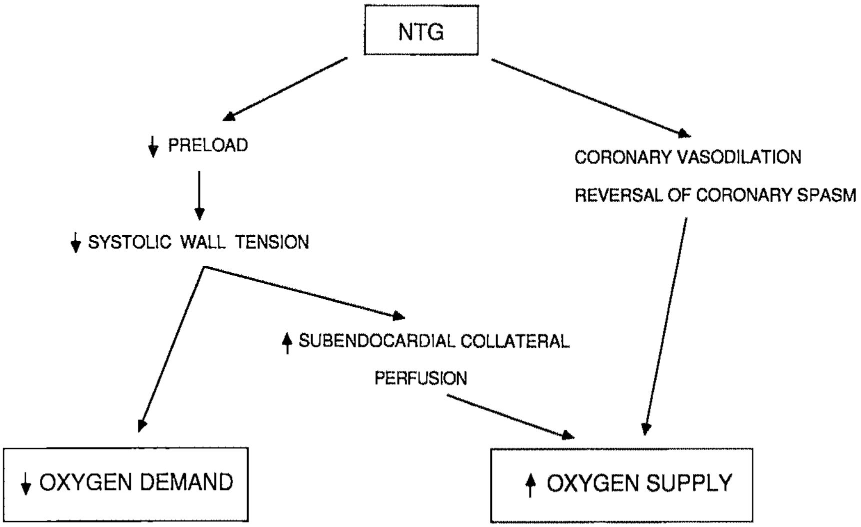

Figure 1. Proposed mechanisms of alleviation of ischemia by nitroglycerin (NTG). (*From* McGregor MM: The nitrates and myocardial ischemia. Circulation 66:689, 1982; with permission.)

episodes[19,32,45] in addition to its coronary vasodilating properties. However, many of the hemodynamic properties of nitroglycerin are shared by anesthetics. Volatile anesthetics cause a decrease in afterload and are coronary vasodilators, in addition to decreasing myocardial oxygen demand directly by cellular effects.[40,95,96] Narcotics decrease pulmonary capillary wedge pressure, hence preload, by venodilation.[59,60,104] Therefore, the anesthetized patient has already experienced some of the physiologic changes by which nitroglycerin may alleviate myocardial ischemia (Fig. 2). Thus, it is not surprising that intraoperative nitroglycerin has been reported to fail to alleviate intraoperative myocardial ischemia.[109] In fact, injudicious use of

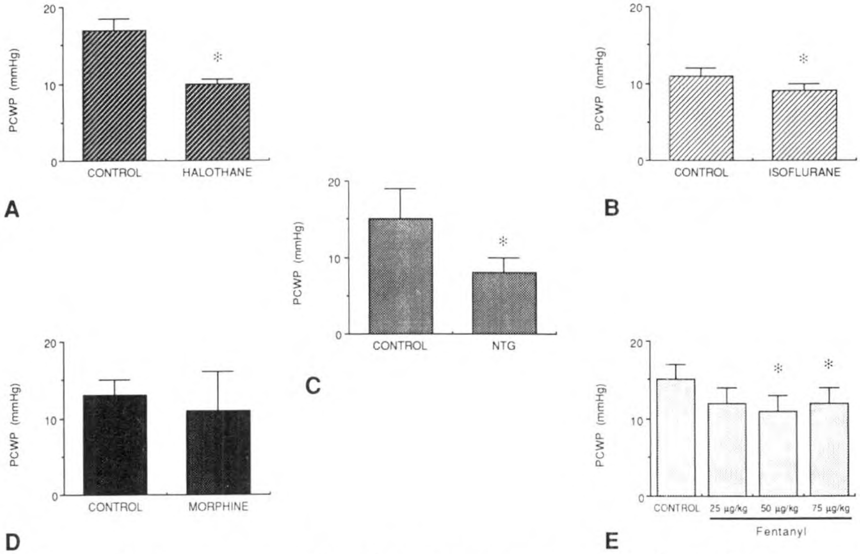

Figure 2. Comparison of the effects of (A) 1 per cent halothane, (B) 1 per cent isoflurane, (C) 62 μg per minute intravenous nitroglycerin, (D) 1 mg per kg intravenous morphine, and (E) intravenous fentanyl on pulmonary capillary wedge pressure (PCWP) in patients with coronary artery disease. Note that all of these drugs cause a similar reduction in PCWP and thus may have similar beneficial effects on myocardial oxygen supply and demand balance. *$P < .05$ versus control. (*Data from* [A] Reiz S, Balfors E, Gustavsson B, et al: Effects of halothane on coronary hemodynamics and myocardial metabolism in patients with ischemic heart disease and heart failure. Acta Anaesth Scand 26:133, 1982; [B] Reiz S, Balfors E, Sorensen MB, et al: Isoflurane—A powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 59:91, 1983; [C] Strauer BE, Scherpe A: Ventricular function and coronary hemodynamics after intravenous nitroglycerin in coronary artery disease. Am Heart J 95:210, 1978; [D] Stoelting RK, Gibbs PS: Hemodynamic effects of morphine and morphine-nitrous oxide in valvular heart disease and coronary-artery disease. Anesthesiology 38:45, 1973; [E] Lunn JK, Stabley TH, Eisele J, et al: High dose fentanyl anesthesia for coronary artery surgery: Plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses. Anesth Analg 58:390, 1979.)

nitroglycerin may result in further decreases in coronary perfusion and thus worsen, rather than improve, myocardial ischemia.

NITROPRUSSIDE

The use of a powerful systemic vasodilator can be of benefit in acute myocardial ischemia and infarction. Decreases in preload and afterload will reduce myocardial oxygen requirements by reducing left ventricular wall tension. Nitroprusside has been successfully employed in the setting of clinical and experimental myocardial infarction, with resultant improvement of myocardial ischemia.[11,21,31,83] Nitroprusside also possesses vasodilating properties similar to nitroglycerin, and thus, nitroprusside can decrease myocardial oxygen demand by decreasing preload and afterload, and increase myocardial oxygen supply by coronary vasodilation.

Two distinct types of vessels exist in the coronary circulation, and both play important roles in myocardial ischemia. The epicardial segments of coronary arteries are relatively large in diameter and serve as conduits, offering little resistance to coronary flow in the normal, undiseased state. The small, intramural coronary arterioles are the major site of resistance to flow and are thought to be the vessels involved in regulation of local myocardial blood flow. With coronary artery disease, dilation of the large conductance type epicardial vessels may increase oxygen supply to an ischemic territory by increasing the amount of flow for a given perfusion pressure, while not affecting the local, intramyocardial distribution of blood flow. However, dilation of the small resistance arterioles may abolish local autoregulation of flow. This may result in further ischemia by decreasing resistance to coronary flow in nonischemic myocardium, in addition to reducing resistance to flow in ischemic territories. Because of the nature of coronary artery disease, epicardial blood flow resistance to ischemic regions is increased. With an indiscriminant decrease in arteriolar resistance throughout the coronary circulation, coronary steal may occur, as blood flow to nonischemic regions is favored owing to less resistance to blood flow in that region.[5,38,115] Many powerful vasodilators, such as chromonar,[38] adenosine,[1] dipyridamole,[6] and isoflurane,[96,100] decrease coronary arteriolar resistance and thus may induce coronary steal.

Vasodilation of the small resistance vessels occurs with nitroprusside,[64] and therefore, nitroprusside is capable of inducing coronary steal. Indeed, nitroprusside significantly worsened electrocardiographically measured injury in patients with acute myocardial infarction and in an experimental model of coronary occlusion, while nitroglycerin alleviated ischemia. Chiariello and coworkers also showed a significant decrease in endocardial blood flow in ischemic regions with the addition of nitroprusside. By contrast, nitroglycerin alleviated clinical ischemia and improved blood flow to the ischemic endocardium.[13] The worsening of ischemia with nitroprusside may reflect indiscriminant vasodilation of coronary conductance and resistance vessels, while nitroglycerin may have improved ischemia by selectively vasodilating the coronary conductance vessels (Fig. 3).

Nitroprusside may be of benefit to patients with perioperative ischemia; however, the marked coronary vasodilation induced by nitroprusside may induce coronary steal and worsening of ischemia. If nitroprusside is employed perioperatively, maintenance of coronary perfusion pressure, in addition to avoiding reflex tachycardia, may prevent or reduce coronary steal-induced ischemia.[6]

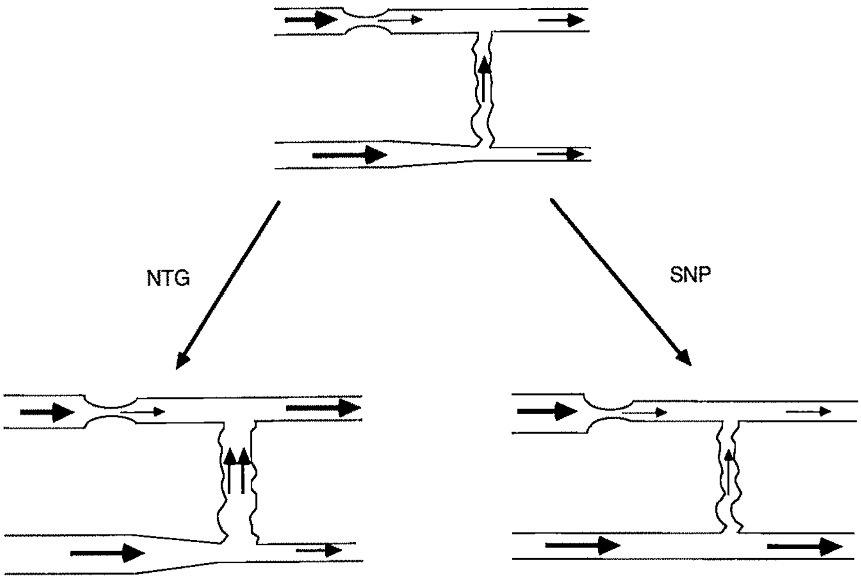

Figure 3. Effects of nitroglycerin (NTG) and sodium nitroprusside (SNP) on coronary collateral blood flow. Distal to the coronary constriction, the coronary vascular bed is fully dilated. Indiscriminant vasodilation of the coronary vasculature by SNP may induce coronary steal, whereas selective vasodilation of conductance and collateral vessels by NTG results in improved blood flow and oxygen supply to the ischemic region.

BETA BLOCKERS

The development of propranolol heralded the beginning of a new era in antihypertensive and antiarrhythmic therapy. Subsequently, a myriad of oral and intravenous beta blockers have been developed and released. Most of these newer agents are designed to minimize the adverse side effects of nonselective beta blockade, while retaining the antihypertensive and antiarrhythmic activity. A subset of beta blockers, those with intrinsic sympathomimetic activity, are partial agonist-antagonists and have little effect on global hemodynamics.

Laboratory studies have shown that administration of practolol or propranolol during acute coronary occlusion resulted in a decrease in ST-segment elevation and transmural necrosis in the ischemic myocardium.[58,94] Mueller and colleagues observed that propranolol decreased the metabolic indices of ischemia in patients with acute myocardial infarction.[74] Propranolol decreased the paradoxical motion of severely ischemic segments and redistributed blood flow to ischemic zones in a laboratory model of acute infarction.[110] Large doses of intravenous propranolol have also been shown to reduce the extent of myocardial injury, measured by enzymatic peaks, in patients with threatened myocardial infarction.[79,86]

With the introduction of the ultra-short acting beta-blocker esmolol, it is now possible to accomplish beta blockade acutely during the perioperative period, with rapid cessation of drug activity when beta blockade is no longer desired, or adverse drug reactions are apparent.[37] Laboratory studies with esmolol also show promise for its use in limitation of infarct size during acute myocardial infarction.[51] Esmolol reduced regional wall motion abnormalities, infarct size, and heart rate when given 15 minutes after coronary occlusion.[54]

The use of beta blockers during anesthesia initially caused concern, as the combined sympatholytic effects of beta blockade and anesthetics were thought to be detrimental. However, the concerns were shown to be unfounded after a series of studies in hypertensive patients showed that beta blockade did not exaggerate the reduction in arterial pressure and cardiac output caused by anesthesia. Beta blockade was found to minimize the hypertensive response to laryngoscopy and endotracheal intubation and to prevent both dysrhythmias and myocardial ischemia.[89] In addition, laboratory experiments demonstrated no adverse interactions between a variety of anesthetics and beta blockers.[30,90] Stone and coworkers examined the effects of a single oral dose of a beta blocker in mildly hypertensive patients presenting for noncardiac surgery. Labetalol, oxprenolol, and atenolol all significantly decreased the incidence of intraoperative myocardial ischemia, as measured by ST-segment changes, possibly due to the beneficial effects of beta blockade in preventing tachycardia and reducing the incidence of acute changes in blood pressure.[105] With the reports of acute angina resulting after abrupt discontinuation of beta blockade,[87] patients now are routinely given long-acting beta blockers on the morning of surgery so as to ensure adequate beta blockade throughout the perioperative period. Although an increased incidence of angina and arrhythmias occurs immediately after drug withdrawal, a large study has shown no increase in long-term mortality after abrupt cessation of low-dose beta blockade.[81]

Large trials examining the protective effect of long-term prophylactic low-dose beta blockers have been somewhat disappointing. Early intravenous beta blockade has been shown to significantly decrease the mortality associated with acute myocardial infarction.[43] The International Study of Infarct Survival (ISIS) trial, which randomly studied 16,000 patients with acute myocardial infarction, found a 15 per cent reduction in mortality after intravenous atenolol. This significant reduction in mortality occurred during the first 24 hours after infarction, but a wide range of confidence limits precluded the authors from making a strong recommendation regarding beta blockade in early myocardial infarction. Furthermore, the magnitude of this decrease in mortality was not in keeping with previous studies showing a marked reduction in enzymatic levels after acute infarction with intravenous beta blockade.[79,86] Long-term beta blockade has been shown to reduce mortality after acute infarction by about 25 per cent (from 10 to 8 per cent total mortality), far lower than one would predict in light of the significant reduction in infarct size observed in experimental studies (Fig. 4). The suggestion is that long-term beta blockade may reduce mortality by affecting factors other than infarct size.[118] Indeed, high doses of propranolol failed to significantly reduce CPK enzyme depletion in myocardium 24 hours after experimental myocardial infarction, although significant reductions in ST-segment depression were seen up to 3 hours after coronary ligation.[85]

Most of the data concerning beta blockade and myocardial ischemia has been obtained from studies involving acute myocardial infarction and/or coronary occlusion. Treatment of perioperative myocardial ischemia, however, may involve allevia-

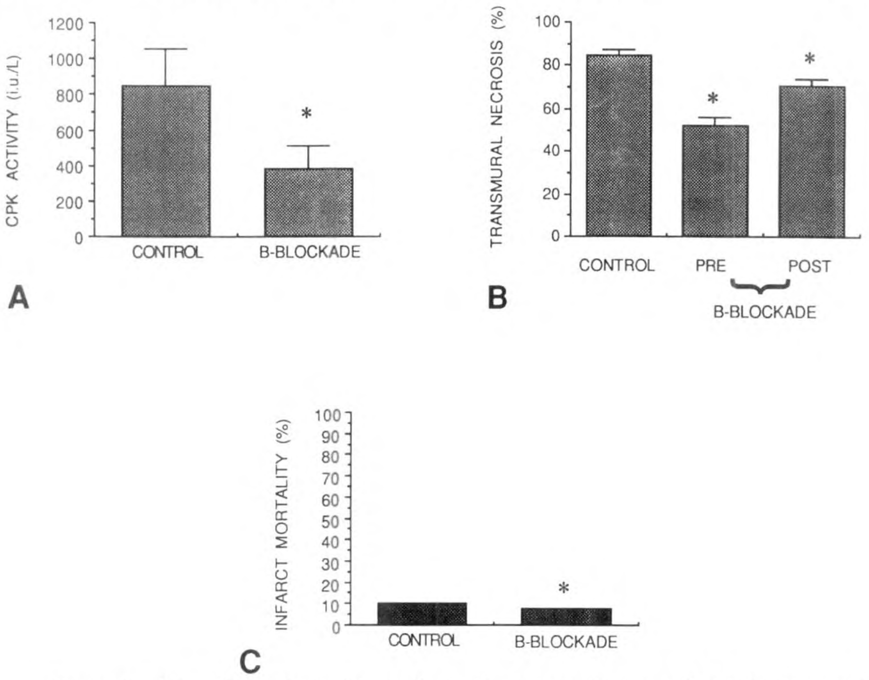

Figure 4. The effect of beta blockade on the extent of myocardial infarction and mortality. (A) In patients with acute myocardial infarction, administration of intravenous propranolol decreases the amount of plasma creatinine phosphokinase (CPK) activity, presumably by decreasing the amount of ischemic myocardium. (B) Pretreatment (PRE) or treatment immediately following experimental coronary occlusion (POST) with intravenous propranolol markedly decreases the amount of transmural myocardial infarction. (C) Despite these dramatic apparent reductions in myocardial damage following myocardial infarction, the results of several large clinical studies do not demonstrate dramatic reductions in infarct mortality by beta blockers. $^*P < .05$ versus control. (*Data from* [A] Norris RM, Clarke ED, Samuel NL, et al: Protective effect of propranolol in threatened myocardial infarction. Lancet ii:907, 1978; [B] Rasmussen M, Reimer KA, Kloner RA, et al: Infarct size reduction by propranolol before and after coronary ligation in dogs. Circulation 56:794, 1977; [C] Yusuf S, Peto R, Lewis J, et al: Beta blockade during and after myocardial infarction: An overview of the randomized trials. Prog Cardiovasc Dis 27:335, 1985.)

tion of ischemia in a territory supplied by a stenosed, but patent, coronary artery. The assumption that this pathologic situation is analogous to the border zone of an acute infarction may be unfounded.[3,24,41,44] Thus, one must examine studies specifically designed to assess the effects of beta blockers on perfused, ischemic myocardium.

Using a laboratory model of critical coronary stenosis, Leone and colleagues showed a significant reduction in regional dysfunction and increase in systolic segmental shortening when intravenous oxprenolol was given under halothane anesthesia.[56] Interestingly, this beta blocker possesses intrinsic sympathomimetic activity and thus alleviated regional ischemic changes without affecting global hemodynamics. However, these investigators induced ischemia by stepwise increases in halothane, rather than increased stress or sympathetic activity, and thus their results may not be directly applicable to perioperative clinical treatment of ischemia. This study suggests that beta blockade during the perioperative period protects against myocardial ischemia and may reverse the deleterious effects of ischemia on regional wall motion. Beta blockade has been shown to redistribute blood flow to the subendocardium, although Vatner et al performed this study in a model of acute coronary occlusion.[110] These and other reports implicate mechanisms other than reduction of heart rate and arterial pressure, possibly mechanisms at the cellular level, as the main beneficial effect of beta blockade in myocardial ischemia.[36,76]

CALCIUM ANTAGONISTS

The introduction of calcium antagonists to clinical practice in the late 1970s represented a new and exciting development in the treatment of myocardial ischemia. Calcium antagonists are effective in treating atrial and nodal arrhythmias, coronary vasospasm, and angina pectoris.[27,71,107] With the recent introduction of diltiazem, three different calcium antagonists are now clinically available.

While all these drugs have calcium channels as a major site of action, each has different effects. In isolated heart muscle, verapamil and nifedipine are potent negative chronotropic agents, while diltiazem is not. However, nifedipine has a greater effect on the baroreceptor reflex system, causing an increase in heart rate and inotropy in intact animals. By contrast, verapamil has little effect on the autonomic nervous system and thus has negative chronotropic and inotropic effects in vivo. Diltiazem has little effect on inotropy, chronotropy, or autonomic reflexes in vitro or in vivo. All three agents increase coronary blood flow by inducing smooth muscle relaxation, with nifedipine being the most potent agent, verapamil next, and diltiazem the least potent. With different chemical structures, it is not surprising that these three calcium antagonists demonstrate distinctly different potencies with regard to physiologic effects. These major differences in effects on vascular smooth muscle, cardiac muscle, and cardiac pacemaker tissue suggest distinct, although interacting, sites of action for each of the calcium antagonists.[70]

All three calcium antagonists protect the myocardium in the face of global cardiac ischemia. Verapamil has been shown to reduce cellular injury, preserve intracellular ATP and energy stores,[78] and enhance recovery of function when given immediately prior to or immediately after global myocardial ischemia.[97] Nifedipine[15,78] and diltiazem [52,116] have effects on myocardial energy stores similar to those of verapamil (Fig. 5).

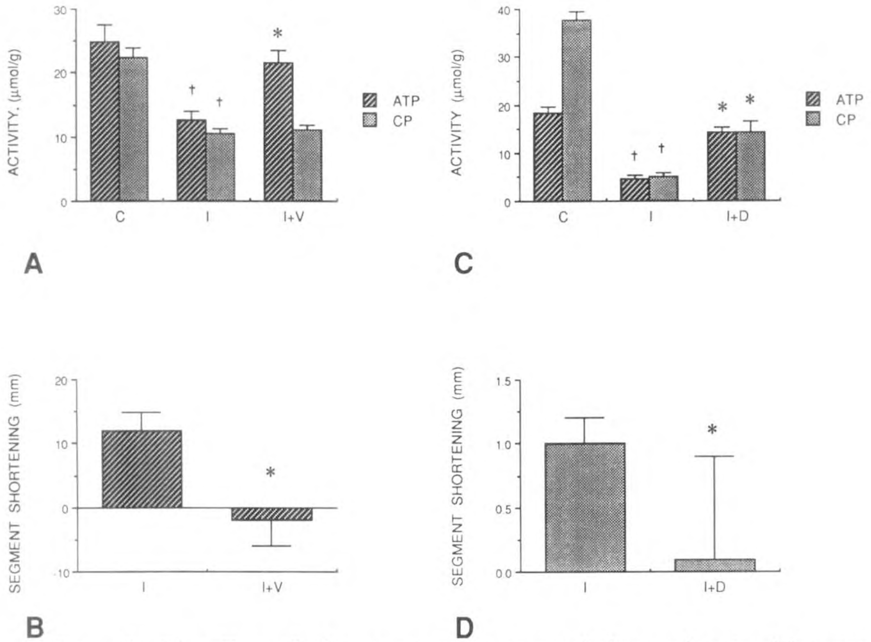

Figure 5. The effects of calcium antagonists on metabolism and regional function in myocardial ischemia. (A) Pretreatment with verapamil prior to global myocardial ischemia significantly attenuates the reduction in ATP caused by ischemia. (B) However, administration of intravenous verapamil during regional (apical) ischemia caused by a reduction in coronary blood flow resulted in profound depression of regional systolic function. (C) Similar to verapamil, diltiazem pretreatment preserved cellular ATP and creatinine phosphate (CP) levels after global myocardial ischemia. (D) However, diltiazem also caused a marked reduction in systolic function when administered during regional ischemia with reduced coronary blood flow. C = control condition; I = ischemia; I + V = intravenous verapamil administration prior to or during myocardial ischemia; I + D = intravenous diltiazem administration prior to or during myocardial ischemia. + $P < .05$ versus C; *$P < .05$ versus I. (*Data from* [A] Nayler WG, Ferrari R, Williams A: Protective effect of pretreatment with verapamil, nifedipine and propranolol on mitochondrial function in the ischemic and reperfused myocardium. Am J Cardiol 46:242, 1980; [B] Smith HJ, Goldstein RA, Griffith JM, et al: Regional contractility: Selective depression of ischemic myocardium by verapamil. Circulation 54:629, 1976; [C] Weishaar RE, Ashikawa K, Bing RK: Effect of diltiazem, a calcium antagonist, on myocardial ischemia. Am J Cardiol 43:1137, 1979; [D] Leone BJ, Philbin DM, Lehot JJ, et al: Intravenous diltiazem worsens regional function in compromised myocardium. Anesth Analg, in press.)

The use of calcium antagonists prior to experimental global myocardial ischemia and reperfusion has been shown to enhance recovery of function and decrease the extent of myocardial injury.[9,52,97,101] Recent work has also commented on preservation of cardiac function and protection of myocardium from ischemia by verapamil in patients during cardiopulmonary bypass and aortic cross-clamping.[2,42,46]

The interactions of calcium antagonists and anesthetic agents, particularly volatile anesthetics, have been intensively studied. The volatile anesthetics can all be considered calcium channel blockers,[61–63] and thus, an adverse interaction between volatile anesthetics and calcium antagonists is possible. Several studies have examined halothane, enflurane, and isoflurane interactions with calcium antagonists in animals with normal coronary anatomy.[47–50,88] In addition, a series of studies has compared the effects of calcium antagonists in awake and anesthetized animals, again without compromised coronary anatomy.[12,68,98] These studies reveal that, while the combination of calcium antagonists and volatile anesthetics depresses myocardial function, this cardiac depression is predictable.

However, the combination of calcium antagonists and volatile anesthetics may have significant effects on regional myocardial function. Intravenous verapamil causes significant regional myocardial dysfunction with both halothane[93] and isoflurane[112] in myocardium supplied by a normal coronary artery. This dysfunction can be reversed by intravenous calcium chloride.[55] The dysfunction seen with the combination of calcium antagonists and volatile anesthetics is qualitatively similar to that seen with ischemia. This similarity suggests that drug-induced cardiac dysfunction may share a common final pathway with ischemia, possibly by disruption of calcium ion fluxes or by alteration of transmural blood flow.

Few studies have examined the effect of calcium antagonists on regional ischemia. Some studies, as with nitroglycerin and beta blockers, examined the effects of calcium antagonists on function in the border zone surrounding a totally ischemic segment of myocardium, while others focused on recovery of function after total ischemia followed by reperfusion. One study examined the effect of verapamil on myocardium supplied by a critically constricted coronary artery.[102] Verapamil caused a significant reduction in systolic function of the compromised area. This result was interpreted by the authors as being cardioprotective, owing to the decrease in energy utilization by the ischemic segment. However, Smith and colleagues cautioned that a verapamil-induced decrease in function of a large area of the left ventricle could seriously compromise left ventricular function. A recent study with halothane, nitrous oxide, and fentanyl anesthesia found similar significant decreases in regional systolic function of myocardium with a compromised blood supply and cardiac output with diltiazem (Fig. 5).[57] Coincident with this decrease in function was a marked increase in postsystolic shortening, a marker of regional ischemia.[23] Thus, regional ischemic dysfunction was substantially worsened when a calcium antagonist was administered; this increase in dysfunction is in keeping with the concept of calcium flux alterations as the critical event in ischemia- and drug-induced regional dysfunction.

VASOCONSTRICTORS

The naturally occurring catecholamines, epinephrine and norepinephrine, have vasoconstrictive properties, while dopamine also causes vasoconstriction when high doses are used. Pure alpha vasoconstrictors, such as methoxamine and phenylephrine, are employed in cardiac anesthesia to increase vascular resistance and thus raise systemic blood pressure. These alpha agonists have vasoconstrictive actions on the coronary circulation, and as such they are thought to have detrimental effects on coronary flow in coronary artery disease. Indeed, evidence of active vasomotor segments in stenotic regions of coronary arteries[8] would suggest that alpha agonists worsen myocardial oxygen supply. Recent evidence, however, suggests that alpha-adrenergic activity may improve transmural myocardial blood flow and thus improve subendocardial ischemia.[25,77]

Descriptions of coronary steal with coronary vasodilators[29,99] led Chiariello and colleagues to investigate the effects of methoxamine on blood flow to ischemic regions in a model of coronary ligation.[14] They found that if coronary perfusion pressure was maintained constant (by controlled hemorrhage), a "reverse coronary steal" occurred with methoxamine. Chiariello and colleagues postulated that this reverse steal was a consequence of vasoconstriction of the normal coronary bed, while the vessels in the ischemic area were not affected by the drug. This may explain the finding of improvement in myocardial ischemia when phenylephrine is added to nitroglycerin in experimental[75] and human[7] studies. However, phenylephrine added to nitroglycerin has also been shown to worsen ischemia in some patients with myocardial ischemia.[18] Come and coworkers treated patients with high initial pulmonary capillary wedge pressures and found improvement with nitroglycerin alone, but reversal of this beneficial effect with the addition of phenylephrine. Borer and colleagues also found slight worsening of ST-segment depression when phenylephrine was added to nitroglycerin therapy in patients with coronary disease and high pulmonary capillary wedge pressures. However, phenylephrine improved ST segments when administered concomitantly with nitroglycerin in patients without evidence of left ventricular failure, that is, those with normal pulmonary capillary wedge pressures (Fig. 6).[7] Thus, in patients with normal left ventricular function, maintenance of coronary perfusion pressure with vasoconstrictors optimizes nitroglycerin's effect on collateral flow to the ischemic territory. However, in patients with evidence of left ventricular failure, nitroglycerin may alleviate ischemia by decreasing preload and opening suben-

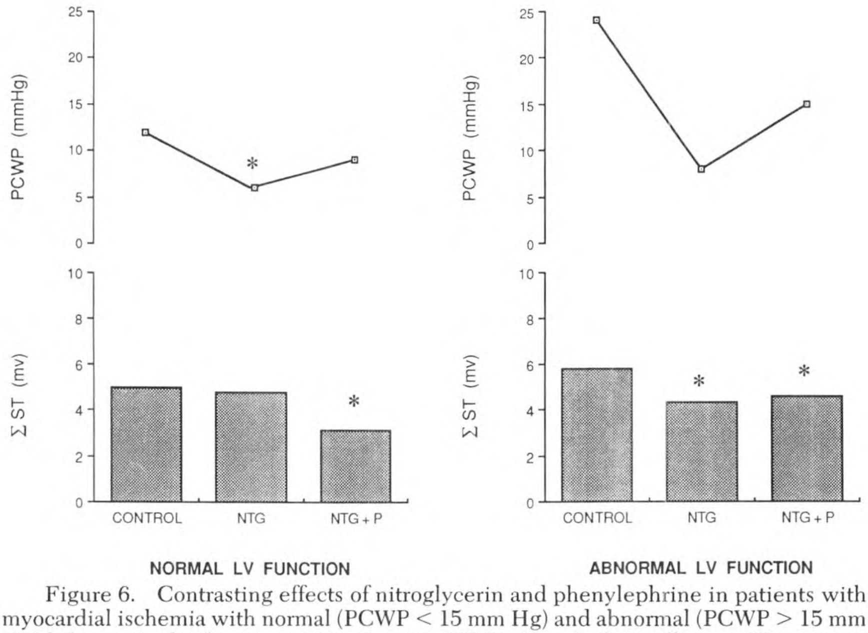

Figure 6. Contrasting effects of nitroglycerin and phenylephrine in patients with myocardial ischemia with normal (PCWP < 15 mm Hg) and abnormal (PCWP > 15 mm Hg) left ventricular function. Nitroglycerin (NTG) alone had no effect on ST-segment depression (ΣST) in patients with normal LV function, yet NTG improved ischemia (decreased ΣST depression) in patients with abnormal LV function. function. The addition of phenylephrine (P) improved ΣST in normal LV function but had no effect on ΣST in patients with abnormal LV function. $^*P < .05$ versus control. (*Data from* Becker LC: Effect of nitroglycerin and dipyridamole on regional left ventricular blood flow during coronary artery occlusion. J Clin Invest 58:1287, 1976.)

docardial collateral vessels to the ischemic regions, while the addition of a vasoconstrictor may have an adverse effect because of the increase in afterload, leading, in turn, to an increase in preload.

ACUTE RIGHT VENTRICULAR FAILURE ASSOCIATED WITH PULMONARY HYPERTENSION

When pulmonary hypertension is present, circulatory failure may be caused by acute right ventricular failure. Relative right ventricular myocardial underperfusion may be a major determinant of this type of circulatory failure.

Coronary blood flow to the right ventricle occurs during both systole and diastole. Kolin et al have shown that left coronary flow is essentially diastolic, while right coronary flow occurs predominantly during ventricular systole (Fig. 7).[53] This is not surprising, since the "coronary driving pressure" (the difference between aortic pressure and right ventricular pressure) is high throughout the cardiac cycle. However, in the

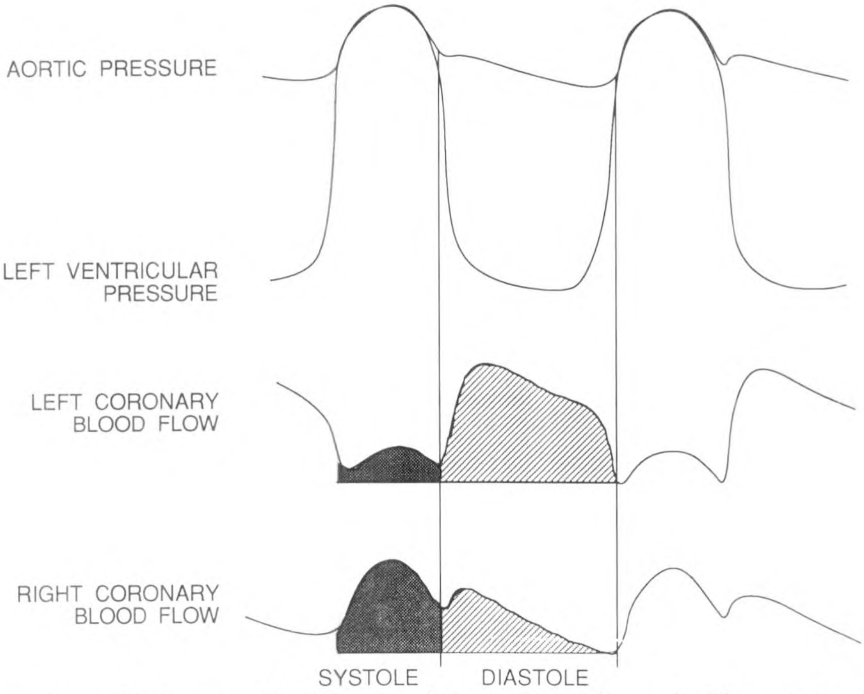

Figure 7. Coronary blood flow in relation to the cardiac cycle. The majority of right coronary blood flow occurs during systole, contrasting with the primarily diastolic left coronary blood flow.

presence of pulmonary hypertension, right ventricular pressure increases, and systolic coronary flow is maintained only as long as aortic pressure is high. It is now recognized that an adequate aortic pressure is essential if right ventricular function is to be maintained in the face of pulmonary hypertension. If this requirement is not met, right ventricular coronary flow will be insufficient to supply enough oxygen to the wall of the right ventricle, and the right ventricle will fail. Vlahakes and colleagues have shown that in the face of progressive constriction of the pulmonary artery, right ventricular myocardial blood flow fails to increase in proportion to oxygen demand.[114] At the onset of right ventricular failure, coronary reactive hyperemia is abolished, indicating the absence of coronary reserve. Phenylephrine, by increasing aortic pressure, increases myocardial perfusion pressure and coronary blood flow and reverses right ventricular failure, as evidenced by an increase in cardiac output.[114] Similarly, in a model of pulmonary microembolization, noradrenaline caused a marked improvement of right ventricular function, while volume overload caused a marked deterioration of right ventricular performance.[35] It must be noted that lung hyperinflation increases the right ventricular afterload and contributes to worsen right ventricular function both in models of pulmonary artery constriction and of microvascular injury.[10] Positive end-expiratory pressure may cause sudden worsening of right ventricular function because of the increase in right ventricular afterload and the reduction in aortic pressure, the latter resulting in poorer right ventricular myocardial perfusion.

While pulmonary vasodilatation with nitroglycerin or prostaglandin E1 can be demonstrated in models of moderate pulmonary hypertension without right ventricular failure,[84] the possibility of systemic hypotension limits their usefulness in patients with pulmonary hypertension,[82] especially as pulmonary vasodilatation is likely to increase intrapulmonary shunting and thus worsen hypoxemia.[113] The addition of a vasoconstrictor has been advocated to enhance the benefits of pulmonary vasodilators.[20] Thus, in patients with acute right ventricular failure associated with pulmonary hypertension, attempts at improving right ventricular perfusion with vasopressors (possibly associated with pulmonary and coronary vasodilators) should precede more complex interventions such as aortic balloon counterpulsation, pulmonary artery balloon counterpulsation,[72] or the introduction of right ventricular assist devices.

INOTROPES

Isoproterenol, norepinephrine, dopamine, and dobutamine, inotropic agents employed for circulatory support in the coronary artery disease patient, possess vasomotor activity. Isoproterenol, by virtue of its beta sympathomimetic activity, markedly increases contractility, yet it significantly worsens ST-segment abnormalities[65] and myocardial contractility[111] after experimental myocardial infarction. Augmented myocardial contractility (and thus increased myocardial oxygen consumption) and coronary steal appear to be the mechanisms by which isoproterenol intensifies ischemia.[17,111] Norepinephrine also augments myocardial contractility, yet it did not result in a loss of segmental contractile activity in ischemic myocardium.[91] However, a comparison of isoproterenol and norepinephrine in patients with cardiogenic shock revealed that both had adverse effects on myocardial metabolism.[73] Dopamine significantly improved contractile function during experimental infarction yet did not induce worsening of epicardial ST-segment elevation in experimental myocardial ischemia, in contrast to isoproterenol,[92] but dopamine was more effective in restoring systolic function to depressed but perfused myocardium rather than acutely ischemic, nonperfused myocardium.[67] Dobutamine, a powerful inotrope with minimal effects on peripheral vascular resistance, caused increases in epicardial ST-segment elevation in experimental infarction[117] and worsening of perfusion in ischemic areas in patients with coronary artery disease.[69] It would appear that norepinephrine and dopamine may be effective in low cardiac output states and result in less myocardial damage than other agents, possibly because of their alpha-adrenergic effects influencing the transmural distribution of coronary flow.[25] However, the experimental results obtained from preparations using acute occlusion of a coronary artery with subsequent administration of various inotropes are difficult to extrapolate to perioperative myocardial ischemia in clinical situations, due to problems with correlations between analysis of border zone function,[3,24,41,44] epicardial ST-segment abnormalities,[4,39,80] lactate production,[103] and the extent and severity of ischemia.

SUMMARY AND CONCLUSION

A wide array of vasoactive agents is now available to the anesthesiologist for protection from and treatment of perioperative myocardial ischemia. Different anesthetic techniques have varying effects on the cardiovascular system, the coronary circulation, and myocardial contractile function. To recommend the use of vasoactive agents in the prevention or treatment of intraoperative myocardial ischemia based on their actions in unanesthetized patients or experimental models, and without considering the consequences of the anesthetic technique employed, would seem imprudent and may lead to worsening of ischemia. Finally, right ventricular physiology and pathophysiology is significantly different from left ventricular physiology, and thus, it is not surprising that treatment of acute right ventricular failure requires interventions that differ significantly from treatment of left ventricular failure.

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Myocardial Protection: Role of Anesthetic Drugs

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A great deal of interest in the influence of anesthetic drugs on myocardial ischemia has arisen in the past two decades as a result of the increasing need for anesthetizing patients with ischemic heart disease for both coronary revascularization procedures and noncardiac surgery. Some work has been done to study and compare various anesthetic agents in many different models of myocardial ischemia, often with conflicting results. No single anesthetic has emerged as the ideal drug for patients at risk for developing myocardial ischemia. Many factors contribute to the complex manner in which anesthetics influence ischemia, including concurrent medical antianginal therapy, state of myocardial function, interaction with the stress response to surgical stimulation, intravascular volume status, and the dynamic regional nature of ischemic heart disease. This article will review some of the available data on the effects of anesthetics on myocardial ischemia and explore their potential role as myocardial protective agents.

GENERAL CONCEPTS

Anesthetics may influence myocardial ischemia by altering the hemodynamic determinants of global myocardial oxygen supply and demand. Drugs that reduce oxygen demand by slowing heart rate, lowering ventricular wall tension, and decreasing contractility, as well as increasing oxygen supply by supporting diastolic coronary perfusion pressure, lengthening

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diastolic time, and decreasing intraventricular pressure can be expected to favorably affect the working heart at risk from ischemia.[47,81] Most anesthetics favorably affect some individual determinants of myocardial oxygen supply and demand, and some unfavorably. The sum of effects on individual variables determines the overall influence on the balance of myocardial oxygen supply and demand.

The effects of anesthetic drugs on the regional distribution of coronary blood flow may have a profound influence on myocardial ischemia. Agents that improve collateral flow to regions supplied by occluded or stenosed coronary arteries are potentially beneficial and those drugs that direct flow away from ischemic regions are potentially harmful. Several arteriolar dilating drugs have been implicated in worsening ischemia because of their ability to unfavorably distribute coronary blood flow away from ischemic regions.[1,21] The effects of inhalational anesthetic agents on regional coronary flow have been recently studied by several investigators with conflicting results. Regional ischemia may also be caused by dynamic coronary vasospasm even in vessels with angiographically visualized coronary lesions.[4,13] Any anesthetic that prevents or attenuates coronary spasm is potentially beneficial.

The release of endogenous catecholamines has been correlated with both the release of the cardiac fraction of creatine kinase (CK-MB) and late mortality in patients with acute myocardial infarction.[34] There is laboratory evidence that norepinephrine is detrimental to ischemic myocardium independent of effects on hemodynamic determinants of myocardial oxygen supply and demand.[18,64,94] Elevated concentrations of catecholamines are associated with increased levels of free fatty acids, which have a toxic effect on ischemic myocardium.[57] Infusion of epinephrine also potentiates thromboxane A_2 release, which may increase platelet aggregation and predispose to coronary thrombosis.[63] Many anesthetics can blunt the release of endogenous catecholamines in response to the stress of surgery,[73] and this may improve myocardial tolerance to ischemia.

An acute ischemic event results in initially reversible and subsequently irreversible processes of cellular damage (see also article by Tinker in this issue). Following the onset of ischemia, tissue levels of high-energy nucleotides decline with time because production from anaerobic glycolysis is unable to keep up with the rate of utilization.[28] The metabolic deficits during ischemia lead to structural changes that culminate in cardiac rigor mortis and cell death.[29,43] The final events that cause irreversible injury and ischemic contracture are not fully understood but sarcolemmal disruption resulting from the action of a calcium-activated protease has been implicated.[30,86] The onset of ischemic contracture can be delayed by interventions that reduce myocardial energy requirements.[22] Beta-adrenergic blocking drugs and calcium entry blockers have been shown to exhibit protective effects in several models of total myocardial ischemia.[8,33,46,92] It is conceivable that those anesthetics that decrease intracellular calcium availability[74] and reduce energy requirements, may also render myocardial cells less vulnerable to ischemic injury.

INHALATION ANESTHETICS

In Vivo Studies

The ability of the volatile inhalation anesthetics to affect the incidence and severity of ischemia has been extensively studied. In many laboratory investigations, halothane and enflurane have been shown to have beneficial effects during myocardial ischemia. Bland and Lowenstein[3] showed that halothane (0.75 per cent), added to a basal intravenous anesthetic, reduced the summation of ST-segment elevation obtained from epicardial electrocardiographic mapping following temporary coronary artery occlusion in dogs (Fig. 1). The improvement in severity of ischemia in these nonfailing canine hearts during halothane administration was associated with a reduction in hemodynamic indices of myocardial oxygen consumption resulting in a more favorable ratio of myocardial oxygen supply and demand.

Smith et al found that both halothane[79] (1.0 per cent) and enflurane[80] (1.5 per cent) improved the ratio of myocardial oxygen availability to consumption in ischemic regions compared with nonischemic regions of nonfailing dog hearts. Both volatile anesthetics were added to a barbiturate 1 hour after coronary artery ligation. The authors postulated that this beneficial effect was the result of a reduction in heart rate.

In isolated, paced rabbit heart preparations, halothane (1.2 per cent) depressed development of myocardial tension relatively less during hypoperfusion than during adequate perfusion.[38] The relative preservation of contractility during ischemia under halothane was accompanied by a decrease in tissue NADH fluorescence, which indicates a beneficial shift in myocardial energy balance.

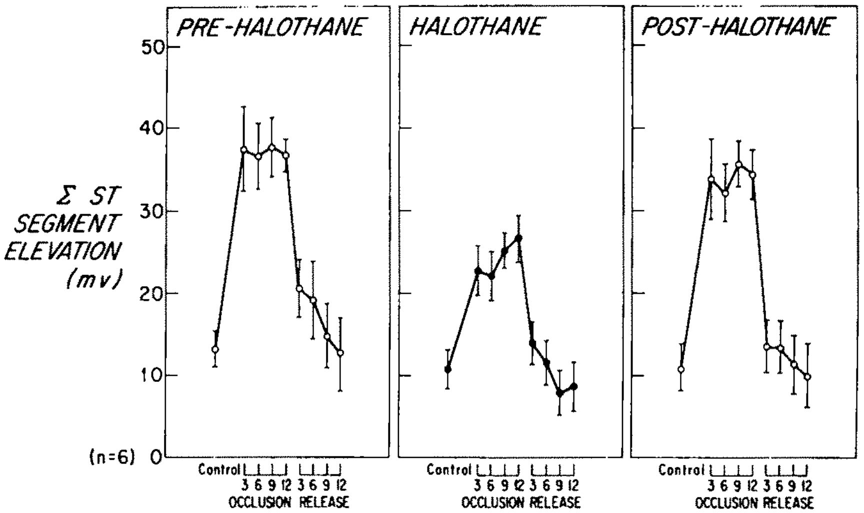

Figure 1. Sum of ST-segment elevations before, during, and after halothane (0.75 per cent) in six dogs. The severity of ischemia produced by occlusion of the LAD coronary artery was less ($P < .001$) during halothane anesthesia. (*From* Bland JHL, Lowenstein E: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. Anesthesiology 45:287–293, 1976; with permission.)

Halothane (0.5 and 1.0 per cent) used as the sole anesthetic reduced the incidence of serious ventricular dysrhythmias and mortality rate following left anterior descending coronary artery ligation in chronically prepared rats.[27,45] Enflurane (1.5 per cent) had an antiarrhythmic effect but did not reduce mortality.[27]

The addition of halothane (0.5 to 1.0 per cent) to barbiturate anesthetized dogs beginning 1 hour after coronary ligation and lasting 12 hours resulted in a 35 per cent reduction of infarct size compared with dogs without halothane (Fig. 2).[11] The halothane-anesthetized dogs had lower heart rates and reduced ventricular contractility. Regional myocardial blood flow measured with radiolabled microspheres was reduced in nonischemic areas proportional to the reduction in demand, but was not reduced in ischemic areas of myocardium in the halothane group.

In dogs anesthetized with chloralose and urethane and subjected to intermittent acute coronary occlusion, halothane (1.1 per cent) reduced ST-segment evidence of ischemia compared with no treatment and to the treatment with propronolol and nitroprusside that produced similar hemodynamic changes.[20] Enflurane (2.2 per cent) added to a barbiturate anesthetic reduced lactate production from ischemic regions following acute coronary artery occlusion in dogs.[89] Heart rate was reduced and mean arterial blood pressure was maintained during enflurane administration.

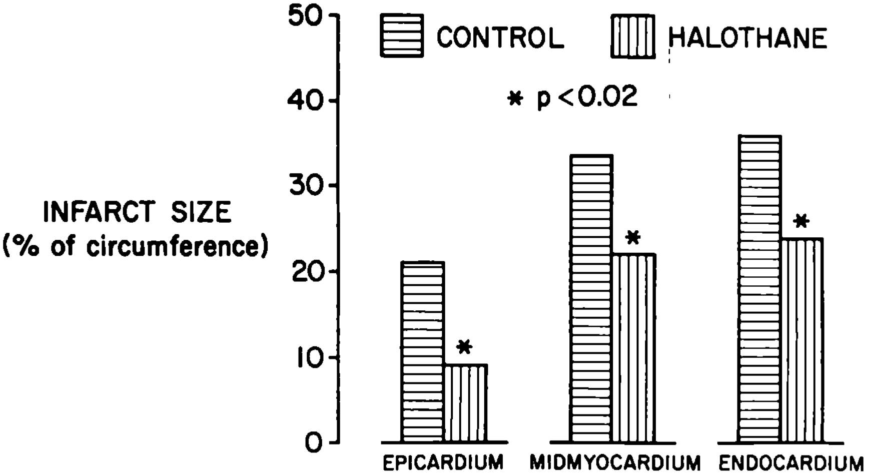

Figure 2. Percentage of the circumference of left ventricle occupied by infarction in epicardium, midmyocardium, and endocardium 24 hours following LAD coronary artery ligation in halothane-treated and awake dogs. The halothane-treated dogs had smaller ($P < .05$) infarcts than the control dogs. (*From* Davis RF, DeBoer LWV, Rude RE, et al: The effect of halothane anesthesia on myocardial necrosis, hemodynamic performance, and regional myocardial blood flow in dogs following coronary artery occlusion. Anesthesiology 59:402–411, 1983; with permission.)

Contrary to these results, several investigations have not produced evidence of a protective effect of volatile agents in animal models of myocardial ischemia. Kissin et al[39] showed that halothane (1.0 per cent) administered to rats for 3 hours following coronary stenosis resulted in a slight increase in average infarct size at 48 hours compared with rats not given halothane. Halothane administration in this study was associated with a reduced mean arterial blood pressure but similar heart rates. Lowenstein et al[44] showed that progressively larger doses of halothane (above 0.5 per cent) accompanied by significant hypotension resulted in evidence of regional ischemic dysfunction in myocardium supplied by a critically stenosed left anterior descending (LAD) coronary artery in dogs. When the left circumflex coronary artery, which supplies a greater portion of myocardium in the dog, was critically stenosed, increasing concentrations of halothane resulted in hypotension, reduced coronary blood flow (Fig. 3), and global dysfunction as well as regional dysfunction.[16]

Merin et al[50] found similar degrees of myocardial lactate production in swine under both halothane (0.5 per cent) nitrous oxide (60 per cent) and fentanyl nitrous oxide (60 per cent) anesthesia following a reduction in LAD coronary blood flow. The halothane group had similar heart rates but lower blood

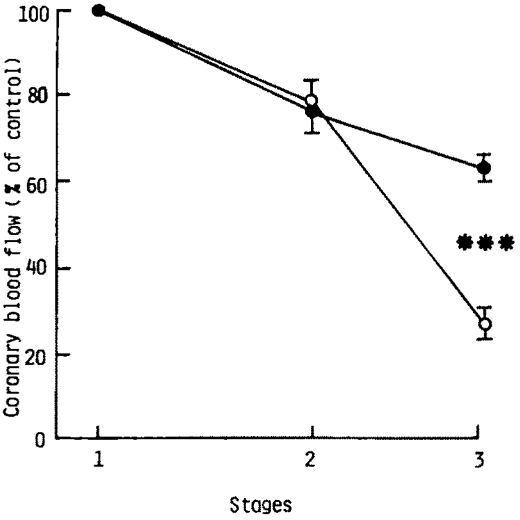

Figure 3. The effect of increasing inspired concentrations of halothane on coronary blood flow before and during left circumflex coronary artery constriction. Before constriction, coronary flow decreased in a dose-related fashion. During constriction, coronary flow decreased markedly with increasing halothane as blood pressure decreased and regional systolic shortening deteriorated. Stage 2 = halothane 1.3 per cent; stage 3 = halothane 1.9 percent; ● = before constriction; ○ = during constriction; *** $P < .005$. (*From* Francis CM, Foex P, Lowenstein E, et al: Interaction between regional myocardial ischemia and left ventricular performance under halothane anesthesia. Br J Anaesth 54: 965–980, 1982; with permission.)

pressures than the fentanyl group. Both groups were given nitrous oxide and pancuronium, which may have affected the results.

Buffington[5] showed that the regional ischemic dysfunction that occurs in dogs following coronary stenosis under halothane anesthesia is determined primarily by hemodynamic determinants of myocardial oxygen supply and demand, and is independent of halothane administration. When blood pressure and heart rate were independently controlled, regional dysfunction occurred with low mean arterial pressures and tachycardia. Halothane itself did not result in regional dysfunctional evidence of worsening ischemia.

Several investigations have failed to demonstrate a beneficial effect of nitrous oxide on myocardial ischemia. When compared with halothane (0.8 per cent), nitrous oxide (75 per cent) failed to preserve coronary autoregulation at low perfusion pressures in barbiturate-anesthetized dogs.[93] Myocardial oxygen consumption, wall tension, and heart rate were less with halothane. Coronary vascular resistances were similar for the two anesthetics, but diastolic intramyocardial tissue pressure was thought to be less in the halothane group resulting in better preserved autoregulation of flow at low pressures.

The replacement of nitrogen with nitrous oxide (67 per cent) as an adjunct to narcotic anesthesia in dogs produced evidence of regional dysfunction in myocardium supplied by an acutely stenosed coronary artery.[60] This effect was not accompanied by hypotension or changes in coronary blood flow. More recent work from the same laboratory resulted in similar findings when nitrous oxide was added to a halothane anesthetic.[65] The appearance of regional dysfunction in nonischemic as well as ischemic areas with the addition of nitrous oxide suggests, however, that the model used may not be specific for ischemic dysfunction.

To summarize the laboratory investigations cited previously, moderate doses of halothane and enflurane may have beneficial effects on ischemic regions of myocardium when the hemodynamic determinants of global myocardial oxygen consumption are reduced and the mean arterial blood pressure is maintained at a reasonable level in the nonfailing working heart (Table 1). When given in doses that produce excessive hypotension or in combinations with drugs that do not lower the heart rate, the volatile agents may be detrimental. Nitrous oxide apparently does not share the potential for protection against ischemia.

Protective effects of isoflurane on myocardial ischemia have not been reported in laboratory investigations similar to those described previously, and there has been recent concern that it may have detrimental effects on the regional distribution of coronary blood flow. Reiz et al[66] reported that 10 of 21 patients with coronary artery disease developed electrocardiographic evidence of myocardial ischemia along with decreased myocardial lactate extraction when anesthetized with isoflurane (1.0 per cent). Global coronary blood flow was maintained

Table 1. *Effects of Inhalation Anesthetics on Animal Models of Myocardial Ischemia*

REFERENCE	DRUG	SPECIES	MODEL	CRITICAL ENDPOINT	EFFECT
Bland[3]	Halothane	Dog	Coronary occlusion	ST-segment elevation	+
MacLeod[45]	Halothane	Rat	Coronary occlusion	Mortality	+
Jang[27]	Halothane	Rat	Coronary ligation	Mortality	+
Davis[11]	Halothane	Dog	Coronary ligation	Infarct size	+
Gerson[20]	Halothane	Dog	Coronary occlusion	ST-segment elevation	+
Kissen[39]	Halothane	Rat	Coronary ligation	Infarct size	–
Lowenstein[44]	Halothane	Dog	Coronary stenosis	Regional function	–
van Ackern[89]	Enflurane	Dog	Coronary occlusion	Lactate production	+
Freedman[17]	Enflurane	Rat	Global ischemia	Post ischemic function	+
Jang[27]	Enflurane	Rat	Coronary ligation	Mortality	0
Philbin[60]	N_2O	Dog	Coronary stenosis	Regional function	–
Ramsay[65]	N_2O	Dog	Coronary stenosis	Regional function	–

+, improved tolerance to ischemia; 0, no change in tolerance to ischemia; –, reduced tolerance to ischemia.

even though perfusion pressure and myocardial oxygen consumption declined significantly, which led to the conclusion that isoflurane produced coronary vasodilation not related to metabolic needs. The abnormal redistribution of coronary flow was thought to contribute to regional myocardial ischemia. Since this report, several laboratory investigations have been performed to study the effects of inhalation anesthetics on coronary blood flow.

In dogs with chronically occluded coronary arteries, perfusion to collateral dependent subendocardial zones, measured by injection of radioactive microspheres, was maintained under halothane anesthesia.[76] Adequate subendocardial perfusion was not, however, maintained during pacing-induced tachycardia. Priebe and Foëx[62] found that isoflurane-induced hypotension, resulting in mean arterial pressures of 70 and 55 mm Hg, produced regional dysfunction in myocardium supplied by critically stenosed coronary arteries. No other anesthetic was compared, and the cause of regional dysfunction may have been due solely to decreased coronary perfusion pressure.

In an elegant study by Sill et al,[75] coronary blood flow, measured by radioactive xenon washout, increased out of proportion to myocardial oxygen consumption as increasing concentrations of isoflurane (0.67, 1.5, and 2.25 per cent) were added to fentanyl-pentobarbital–anesthetized dogs. Cross-sectional areas of large epicardial coronary arteries determined by quantitative angiography did not change, indicating that isoflurane dilated small intramyocardial arterioles in a dose-related manner. Arteriolar dilation has the potential for developing regional ischemia in collateral dependent myocardium.[1,21] A previous investigation by Merin,[51] however, revealed no evidence of a difference in coronary arteriolar dilation between dogs anesthetized with 1.6 and 3.2 per cent isoflurane. Measurements of coronary flow in Merin's study were made at low levels of myocardial oxygen consumption and did not compare coronary flow and oxygen consumption in dogs with no isoflurane.

Gelman et al[19] found that isoflurane (1.0 and 2.0 MAC) increased coronary blood flow despite lower perfusion pressures and cardiac outputs in normal dogs (Fig. 4). Halothane was associated with a reduction in coronary flow proportional to the fall in myocardial oxygen demands.

Buffington et al[6] compared the effects of halothane, isoflurane, adenosine, and nitrous oxide on regional coronary flow in a dog model of ischemia in which the LAD coronary artery was chronically stenosed and circumflex coronary flow and perfu-

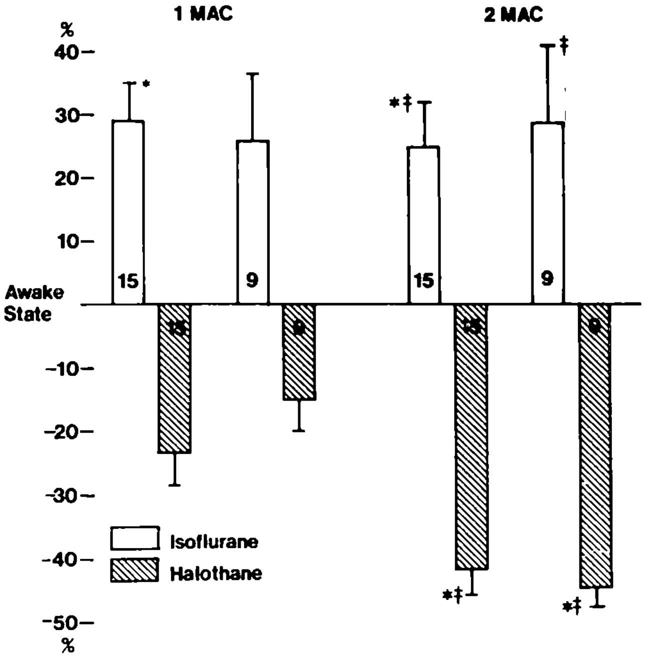

Figure 4. Per cent changes in myocardial blood flow during halothane and isoflurane anesthesia. *$P < .05$ versus control; †$P < .05$ versus 1 MAC; ‡$P < 0.5$ isoflurane versus halothane. (*From* Gelman S, Fowler KC, Smith LR: Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 63:557–565, 1984; with permission.)

sion pressure could be controlled. All dogs were anesthetized with morphine and α-cloralose. When circumflex perfusion pressure (90 mm Hg), heart rate (100 bpm), and mean arterial pressure (60 mm Hg) were held constant, both isoflurane (1.46 per cent) and adenosine increased coronary flow by lowering coronary resistance. Nitrous oxide (70 per cent) and halothane (0.87 per cent) did not change coronary resistance or flow. Under conditions of moderately reduced circumflex coronary flow (35 ml per 100 g per minute), the addition of isoflurane resulted in a redistribution of blood flow from collateral dependent zones to normal myocardium, and from subendocardium to subepicardium. Halothane did not affect the regional distribution of coronary perfusion. Systolic thickening was impaired in collateral dependent myocardium by the addition of isoflurane but not halothane. The addition of isoflurane in this model of critical coronary stenosis adversely affected coronary perfusion of the collateral dependent zone at risk and resulted in regional ischemic dysfunction. Collateral circulation and regional function were not impaired by halothane.

A more recent study by Cason et al,[7] also using a canine model of chronic LAD stenosis with collateral vessel development, failed to show evidence of adverse changes in coronary vascular resistance or abnormal redistribution of flow when either halothane (0.5 or 1.5 MAC) or isoflurane (0.5 or 1.5 MAC) were added to a fentanyl-pentobarbital anesthetic. There was a slight increase in coronary sinus oxygen content and a decrease in left ventricular oxygen extraction during isoflurane (1.5 MAC), indicating that normal autoregulation may have been disturbed. Cason's dogs were studied under conditions of much higher coronary flow than Buffington's moderate flow reduction[6] (51 versus 35 ml per 100 gram per minute) and were thus at much less risk of developing regional ischemia. In a related study from the same laboratory,[23] halothane, enflurane, and isoflurane, at concentrations of 1 MAC, all caused a reduction of left circumflex coronary autoregulation and an increase in coronary sinus oxygen content. The changes were greater with isoflurane but much less than were found with the potent vasodilator adenosine.

In one outcome study, swine, both with and without a critical coronary stenosis, given increasing doses of either halothane or isoflurane, required a larger dose of isoflurane (relative to MAC) to result in death.[72] Although the authors concluded that isoflurane has a greater margin of safety than halothane in swine with critical coronary stenosis, the presence or absence of a coronary stenosis had no effect on the fatal dose. Application of this data to the question of anesthetic effects on myocardial ischemia is unclear.

There can be little doubt that the bulk of laboratory evidence in animal models indicates that isoflurane can dilate small coronary arterioles. Under some circumstances dilation of arterioles in normal myocardium may potentiate regional ischemia in vulnerable collateral dependent myocardium. Halothane appears not to cause adverse redistribution of coronary flow. The relevance of these animal models and experimental conditions to clinical settings is discussed in the article by Tinker in this issue.

In Vitro Studies

There is some laboratory data to indicate that volatile anesthetics may influence myocardial tolerance to ischemia apart from effects on hemodynamics or collateral coronary circulation. Isolated rat hearts perfused with a buffer saturated with enflurane (2.0 per cent), subsequently made globally ischemic until the onset of contracture, and then reperfused, demonstrated a greater recovery of function than hearts perfused with buffer alone.[17] Hearts treated with enflurane prior to ischemia also exhibited greater stores of ATP following reperfusion, suggesting that enflurane may enhance tolerance to ischemia. Halothane-anesthetized dogs placed on cardiopulmonary bypass, subjected to 60 minutes of normothermic global ischemia, and then reperfused, released less CK-MB isoenzyme than dogs anesthetized with α-chloralose, indicating improved tolerance to total ischemia.[15] It has recently been shown that the time required for development of irreversible rigor in the isolated totally ischemic left ventricle was delayed in dogs anesthetized with halothane (2.0 MAC) compared with isoflurane (2.0 MAC).[24] Tissue stores of ATP were better preserved in the halothane group, leading the authors to conclude that halothane influences cellular metabolism in a way that renders myocardial tissue less vulnerable to ischemic injury, independent of effects on hemodynamics.

Clinical Studies

The occurrence of myocardial ischemia detected by ECG,[78] lactate production,[95] and thallium perfussion scans[40] is common during clinical anesthesia and surgery for patients with significant ischemic heart disease. The incidence of ischemia has been associated with tachycardia[42,78] and hypotension,[42] but often is not related to hemodynamic changes.[40,42,95]

Moffitt et al conducted a series of clinical investigations to determine the effects of halothane,[52] enflurane,[53] and isoflurane[54] on myocardial metabolism and hemodynamics in patients with significant coronary artery disease and good left ventricular function undergoing coronary artery revascularization. Twelve patients were given halothane with either intravenous thiopentol or following intramuscular morphine. Mean arterial pressure declined 17 and 30 per cent, as did myocardial oxygen consumption. Coronary sinus oxygen content increased. Intubation caused an increase in blood pressure to above awake levels. One of 12 patients showed myocardial lactate production indicating ischemia.[52] Ten patients receiving beta-blockers, were anesthetized with enflurane in doses to initially depress blood pressure by 30 per cent, and then to maintain it slightly below awake levels during stimulation. Coronary blood flow remained proportional to myocardial oxygen consumption and no patient developed myocardial lactate production.[53] Of ten patients on beta-blocker therapy anesthetized with isoflurane in a similar protocol, average coronary vascular resistance and myocardial lactate extraction was reduced. Lactate production, indicating the presence of ischemia, was evident in three of the ten patients.[54] Patients anesthetized with combinations of halothane and fentanyl or enflurane and fentanyl in a similar fashion developed myocardial lactate production one out of ten times in both groups.[55]

In clinical studies of myocardial metabolism in both healthy patients[82] and patients with ischemic heart disease and moderate heart failure,[67] halothane did not affect coronary vascular resistance. Myocardial oxygenation was adequately maintained in both groups without evidence of myocardial lactate production. Low levels of myocardial damage, estimated by CK-MB release, were found in patients having coronary revascularization when anesthetized with either halothane or enflurane.[71]

As mentioned previously, Reiz found that isoflurane administered to patients with ischemic heart disease reduced coronary vascular resistance when given as the sole anesthetic[66] or in combination with nitrous oxide.[68] Myocardial lactate extraction was significantly reduced in both groups. ECG evidence of ischemia occurred in 10 of 21 patients with isoflurane alone and in 7 of 13 patients when isoflurane was used in combination with nitrous oxide.

In other circumstances isoflurane has had a protective influence on ischemia. Tarnow et al[87] found that isoflurane (0.5 per cent) and nitrous oxide (50 per cent) increased the threshold for the development of pacing-induced myocardial ischemia in patients with multi-vessel coronary artery disease. No other anesthetic was tested so a comparison of agents in this setting is not possible.

The clinical data in humans with coronary artery disease indicates that halothane and enflurane can be used as the primary anesthetic with a reasonably low incidence of myocardial ischemic events (Table 2). The association of ischemia with reduced coronary vascular resistance reported in several, but not all, human studies indicates that isoflurane may produce unfavorable coronary flow distribution in some patients with ischemic heart disease as it does in some laboratory preparations.[6,62,75]

INTRAVENOUS ANESTHETICS

Laboratory Studies

The effects of intravenous anesthetic agents on myocardial ischemia have not been as extensively studied in the laboratory

Table 2. *Incidence of Ischemia in Humans with Coronary Disease Under Inhalation Anesthetics*

REFERENCE	DRUG	CRITICAL ENDPOINT	INCIDENCE (%)
Moffitt[52]	Halothane	Lactate production	8.3
Reiz[67]	Halothane	Lactate production	0.0
Moffitt[53]	Enflurane	Lactate production	0.0
Moffitt[54]	Isoflurane	Lactate production	30.0
Reiz[66]	Isoflurane	ECG changes	47.6
Reiz[68]	Isoflurane-N_2O	ECG changes	53.9
Tarnow[87]	Isoflurane-N_2O	Pacing-induced ECG changes	Threshold for ischemia improved

as have the inhalation agents. The influence of barbiturates and fentanyl on infarct size and metabolism in animals following acute coronary stenosis has, however, been evaluated in several investigations.

A single dose of thiopental (10 mg per kg) administered to dogs 10 minutes following left circumflex coronary artery ligation was associated with increased infarct size relative to the amount of tissue supplied by the occluded vessel.[31] Those animals given thiopental had significantly higher heart rates than a conscious control group given saline. When conscious dogs were paced at heart rates equal to the thiopental group, infarct size was increased to a similar degree. Infarct size was also increased in pentobarbital-anesthetized dogs compared with conscious dogs in a related study by the same investigator.[32] Total catecholamine levels, as well as heart rates, were elevated in the pentobarbital group. Reduction of heart rate in the pentobarbital-anesthetized dogs by sinoatrial node destruction resulted in reduced infarct size.

In a three-way comparison of drug effects on myocardial infarction in ventilated barbiturate-anesthetized dogs, the addition of fentanyl (100 μg per kg) resulted in smaller infarctions following coronary artery ligation compared with pentobarbital (30 mg per kg) or halothane (0.9 per cent).[49] Infarct size was directly related to heart rate in all three groups and the fentanyl group exhibited the lowest overall heart rate.

Myocardial production of lactate following repetitive coronary stenosis was reduced by the addition of fentanyl (25 μg per kg) to a barbiturate-nitrous oxide anesthetic.[90,91] Fentanyl was associated with a lower heart rate. Rapid pacing reduced the beneficial effect of fentanyl.[90] Myocardial release of potassium and hydrogen ions, and utilization of free fatty acids was also reduced by the addition of fentanyl.[91] Merin,[50] as mentioned earlier, found a similar degree of myocardial lactate production following a reduction in coronary flow in swine whether under a halothane-nitrous oxide or fentanyl-nitrous oxide anesthetic. Myocardial oxygen consumption was less but heart rate greater in the halothane group.

From these investigations using animal models of ischemia, it is apparent that intravenous agents may improve tolerance to an ischemic insult when heart rate is slowed and may have detrimental effects if the heart rate is increased. There is also one preliminary report from an investigation of dogs anesthetized with sufentanil (100 μg per kg) that showed that the time required for excised left ventricular tissue to develop rigor in the absence of coronary circulation or wall stress was inversely related to preischemic norepinephrine levels.[25] It was concluded that anesthetics have the potential to improve myocardial tolerance to ischemia by diminishing the adrenergic stress response to surgery, independent of effects on hemodynamics.

In studies involving animals with normal coronary circulation, thiopental (10 mg per kg) increased myocardial oxygen consumption primarily by increasing heart rate while depressing contractility.[58] Coronary vascular resistance was decreased. Etomidate (0.8 and 1.6 mg per kg) had little effect on myocardial oxygen consumption or coronary flow.[58,61] The regional distribution of coronary blood flow and myocardial metabolism of lactate and free fatty acids remained unchanged by etomidate.[61] Diazepam (2 mg per kg) was found to decrease heart rate, myocardial contractility, myocardial oxygen consumption, and systemic vascular resistance.[10] Total coronary blood flow was increased, however. Regional distribution of coronary flow was not studied.

Human Studies

The effects of intravenous anesthetic agents on myocardial oxygen consumption and coronary blood flow in humans with coronary artery disease have also been investigated (Table 3). Sonntag et al[83] found that fentanyl (100 μg per kg) administered following intubation with etomidate and pancuronium, produced a 10 per cent reduction in coronary blood flow that paralleled a 14 per cent reduction in myocardial oxygen consumption. Five of nine patients, however, experienced myocardial lactate production, indicating ischemia. Fentanyl failed to adequately blunt the hemodynamic responses to surgery and seven of nine patients produced myocardial lactate during sternotomy. Other investigators have not found such a high incidence of ischemia with fentanyl. In patients undergoing coronary re-

Table 3. *Effects of Intravenous Agents on Myocardial Oxygen Consumption and Blood Flow in Healthy Humans*

REFERENCE	DRUG	DOSE	MVO_2 (%)	CORONARY BLOOD FLOW (%)
Sonntag[83]	Fentanyl	100 μg/kg	−14	−10
Moffitt[56]	Fentanyl	109 μg/kg	−29	−32
Lappas[41]	Sufentanil	10–30 μg/kg	−17	−13
Côté[9]	Diazepam	5–8 mg	−15	−8
Ikram[26]	Diazepam	0.1 mg/kg	Not given	+73
Marty[48]	Midazolam	0.2 mg/kg	−26	−24
Kettler[36]	Etomidate	0.12 mg/kg/min	+6	+19
Patschke[59]	Etomidate	0.3 mg/kg	−14	Not given
Sonntag[84]	Thiopental	4 mg/kg	+55	+55
Reiz[70]	Thiopental	6 mg/kg	−39	−33
Sonntag[85]	Ketamine	5 mg/kg	+63	+67
Balfors[2]	Ketamine	2 mg/kg	+50	+48

vascularization, fentanyl (109 μg per kg) was associated with a proportional reduction of coronary blood flow (32 per cent) and myocardal oxygen consumption (29 per cent).[56] Only one of ten patients exhibited myocardial lactate production. Skourtis et al[77] found myocardial lactate production in one of six coronary surgical patients given fentanyl as the primary anesthetic. When combined with droperidol and nitrous oxide, fentanyl (15 μg per kg) produced similar declines in both myocardial blood flow and oxygen consumption without any evidence of lactate production or ECG signs of ischemia in eight coronary patients.[69]

When sufentanil was used as the primary anesthetic in doses of 10, 20, or 30 μg per kg, Lappas et al[41] found minimal changes in coronary blood flow or myocardial oxygen consumption. Myocardial lactate production occurred in 2 of 20 patients with coronary disease.

The benzodiazepines have been shown to have either dilating effects or little influence on coronary vascular resistance in various investigations of patients with coronary artery disease. Côté et al[9] showed that diazepam (5 to 8 mg) reduced left ventricular diastolic pressure 26 per cent accompanied by a slight decrease in coronary blood flow (−8 per cent) and myocardial oxygen consumption (−15 per cent). There was no change in coronary vascular resistance and no new myocardial lactate production in 12 patients. Midazolam (0.2 mg per kg) moderately lowered coronary blood flow (−24 per cent) and myocardial oxygen consumption (−26 per cent) without changing coronary vascular resistance in a similar study.[48] There was no myocardial lactate production or ECG evidence of ischemia in any of the eight patients. Ikran et al,[26] however, found diazepam (0.1 mg per kg) to markedly increase coronary blood flow. The incidence of ischemia or the possibility of adverse redistribution of coronary flow was not reported.

Thiopental (4 mg per kg) caused a large increase in heart rate and myocardial oxygen consumption (+55 per cent), which was matched by an equal increase in coronary blood flow in patients without coronary artery disease.[84] Patients with a limited ability to increase flow because of coronary stenosis may not, however, be able to meet the increased demand. Reiz et al,[70] in contrast, found that thiopental (6 mg per kg) reduced myocardial oxygen consumption, although myocardial lactate extraction was decreased indicating the possibility of ischemia.

Etomidate infusion (0.12 mg per kg per minute) resulted in no change in myocardial oxygen consumption and a slight increase (+19 per cent) in coronary blood flow in five vascular surgery patients.[36,37] Etomidate was found to have the least effect on hemodynamic determinants of myocardial oxygen balance compared with methohexital, propanidid, ketamine, althesin, or droperidol. Patschke et al[59] found that etomidate (0.3 mg per kg) caused a slight decrease in myocardial oxygen consumption (−14 per cent) in healthy patients. Effects of etomidate on myocardial blood flow and oxygen consumption in patients with known ischemic heart disease is unknown, but it was found safe as an induction agent in patients having acute myocardial infarction.[35] Ketamine is associated with marked increases in myocardial oxygen consumption, which must be met by increased coronary flow and is potentially dangerous in patients with compromised coronary circulation.[2,85]

SUMMARY AND CONCLUSION

Most anesthetic techniques can conceivably have favorable effects on myocardial ischemia in certain circumstances by reducing the hemodynamic and neurohumoral stress response to pain, anxiety, and surgical trauma.[12,14] There is no one ideal anesthetic drug or technique for all situations and there are many complicating factors that may influence whether or not a specific drug has the potential to protect against ischemia. These include interactions with other drugs,[88] the magnitude of the stress response to surgery, the degree of myocardial damage, the presence of coronary spasm, and the degree of collateral coronary circulation.

Of the inhalation anesthetics, halothane and enflurane demonstrate protective effects on the nonfailing ischemic heart in animals when excessive hypotension is avoided. In patients with coronary artery disease they are associated with a low incidence of myocardial ischemia when sensitive methods of detection are used. Isoflurane may not be the drug of choice for patients with ischemic heart disease because of its potential for causing the adverse redistribution of coronary flow.

Because they either decrease or have minimal effects on myocardial oxygen consumption, fentanyl, sufentanil, diazepam, midazolam, and etomidate are the intravenous agents most likely to favorably influence myocardial ischemia. None are complete anesthetics by themselves and thus have the potential to inadequately blunt the stress response to surgery or laryngoscopy. They are probably more effectively used in combinations with each other or with an inhalation anesthetic during periods of stimulation.

We currently have a great deal of knowledge about how the anesthetic agents affect hemodynamic determinants of myocardial oxygen consumption and supply. It is well recognized that the use of anesthetic drugs to limit myocardial oxygen consumption while avoiding excessive decrements in supply has the potential to reduce the incidence of and improve tolerance to myocardial ischemia. Further work needs to be done to determine how anesthetic agents affect the occurrence of coronary vasospasm, how they influence intracellular metabolism during myocardial ischemia, and whether they have any effect on coronary thrombosis.

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Myocardial Ischemia and Perioperative Infarction 0889-8537/88 $0.00 + .20

Treatment of Myocardial Ischemia and Infarction

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Increasing numbers of patients with ischemic heart disease are presenting to the operating room for noncardiac and cardiac surgery. Anesthesiologists caring for these patients must be prepared to participate in the treatment of ischemia and infarction. Myocardial ischemia develops as a result of an imbalance between myocardial oxygen supply and demand. If left untreated, myocardial infarction evolves. It has been shown that intervention during this period can be potentially beneficial or detrimental.[66] Control of oxygen demand by limiting increases in heart rate, blood pressure, preload, and contractility is now possible with a variety of anesthetic drugs and pharmacologic methods. Equally important is the manipulation of oxygen supply and redistribution of blood flow to ischemic regions so that maximal myocardial salvage can be realized. The foundation of medical therapy has included nitroglycerin, beta blockers, and calcium channel blockers. For refractory ischemia the intra-aortic balloon pump and metabolic substrate therapy have been successful. Future directions in this area may involve the use of oxygen free-radical scavengers to limit ischemic damage.

However, as pointed out by Slogoff and Keats during anesthesia for coronary artery bypass graft (CABG) surgery, as many as half of all episodes of perioperative ischemia may not be preventable by simply providing optimal hemodynamic indices of myocardial oxygen supply and demand.[94] They further postulate that new intraoperative ischemia, both hemodynamically related and unrelated, may only serve to identify a subset of patients more likely to have postoperative myocardial infarction

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without any cause and effect relationship between the individual ischemic episodes and the postoperative infarction.[94]

NITROGLYCERIN

In 1968, Viljoen[98] administered nitroglycerin intramuscularly and in 1976, Kaplan et al demonstrated its effectiveness intravenously during coronary artery bypass surgery.[35] Since then, its application has grown immensely. Nitroglycerin (NTG) is the prototype nitrate and works by interacting with the sulfhydryl groups of the nitrate receptor.[2] This leads to the formation of nitric oxide, which ultimately leads to activation of guanylate cyclase. This enzyme catalyzes the formation of increasing amounts of cGMP. cGMP may then cause vascular smooth muscle relaxation (Fig. 1).[4,40] Calcium flux may be disturbed, and this may lead to relaxation of vascular smooth

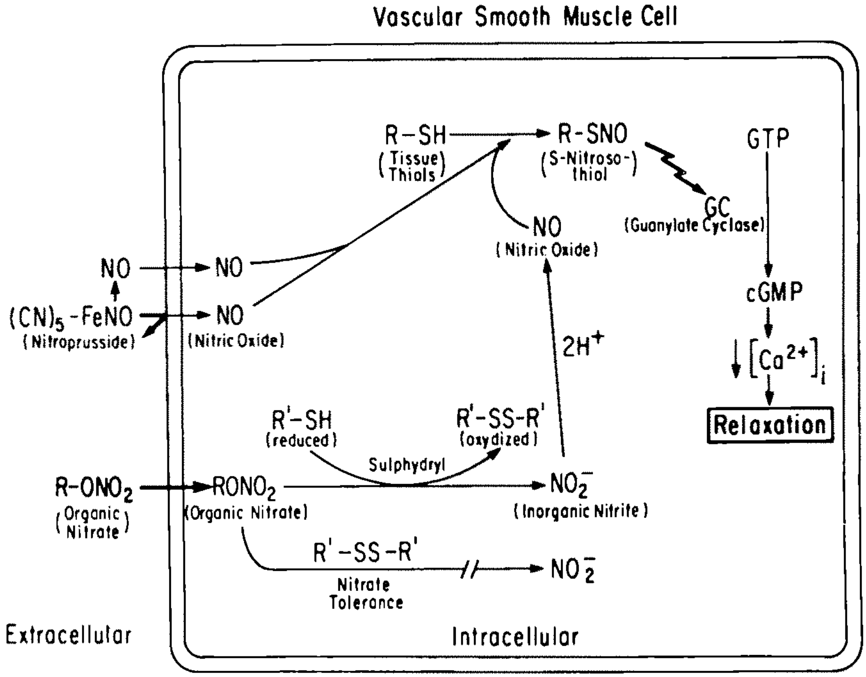

Figure 1. Cellular mechanism of action of nitroglycerin ($R-ONO_2$) and nitroprusside ($(CN)_5$-FeNO). Different pathways lead to a decrease in "available" intracellular calcium via activation of guanylate cyclase. The proposed mechanism of nitrate tolerance is illustrated by depletion of reduced sulphydryl groups (R-SH). (*Modified from* Ignarro, et al: Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrites, nitroprusside and nitric oxide: Evidence for the involvement of S-nitrosothiols as active intermediates. J Pharmacol Exp Ther 218:739–749, 1981; with permission.)

muscle.[21] Cyclic GMP may also modulate the release of endothelial-derived relaxation factor.[68] The phenomena of nitrate tolerance may be secondary to diminished amounts of reduced thiol groups within cells leading to decreased production of cGMP.[46] A portion of the vasodilator action of nitroglycerin may be mediated by its effect on prostaglandin metabolism. Nitroglycerin may cause an increase in the vasodilator prostacyclin, a potent coronary vasodilator.[54]

The primary cardiovascular action of nitroglycerin is vasodilation, which by reducing preload and to a lesser extent afterload, decreases myocardial oxygen consumption. However, reflex increases in heart rate and contractility may limit this reduction in oxygen consumption. For this reason combination therapy with beta-adrenergic blockers may limit this reflex.[37] Nitroglycerin also produces an increase in subendocardial blood flow by decreasing left ventricular end-diastolic pressure (LVEDP) to a greater extent than aortic diastolic blood pressure and thereby improving coronary perfusion pressure (Fig. 2).[38] Nitroglycerin works by primarily dilating the conductive portions of the coronary circulation.[7] In human studies, intravenous NTG in doses of 75 to 100 μg has been shown to increase the diameter of the left anterior descending and circumflex coronary arteries, as well as collateral vessels.[7,19] In contrast, sodium nitroprusside may decrease collateral flow and produce a "steal" by dilating the arteriolar vessels.[62] Ludbrook et al showed that nitrates also improve diastolic compliance of the ischemic heart.[59]

It is believed that when administered intravenously, the

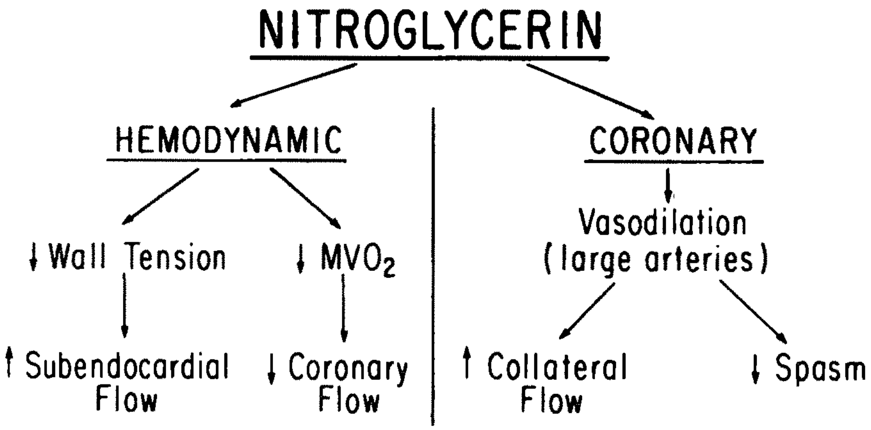

Figure 2. Nitroglycerin influences myocardial blood flow indirectly by hemodynamic changes and by direct effects on coronary blood vessels.

antianginal effects of NTG are primarily due to a decrease in global myocardial oxygen demand rather than an increase in coronary blood flow.[47,55] When given via the intracoronary route, systemic effects are limited but there is an increase in flow to ischemic tissue, a reduction in ST-segment elevation, and an improvement of systolic function and diastolic compliance.[7,56]

Nitrates are the principal form of medical treatment for angina. Relief of anginal pain is accompanied by an improvement in ST-segment changes, in regional and global wall motion, and ejection fraction.[91] Coronary spasm may be present preoperatively as both a component of stable and unstable angina.[79] It may also occur intraoperatively and postoperatively, especially after myocardial revascularization.[10] Intracoronary NTG doses of 25 to 100 μg have been shown to relieve coronary spasm that occurred spontaneously or after ergonovine provocation in the cardiac catheterization laboratory.[77] Buxton et al and Cohen et al have recommended 0.1 to 1.0 mg of intracoronary NTG for relief of spasm after CABG that was refractory to intravenous NTG.[10,14] Acutely, the effects of intravenous NTG may be potentiated by sublingual nifedipine.[14]

Preoperative nitrate therapy should be continued to prevent decreased cardiac output, increased systemic vascular resistance, increased sensitivity to vasoconstrictors, and rebound myocardial ischemia.[2]

Kaye et al showed that intravenous NTG improved the endocardial viability ratio prior to CPB in patients undergoing CABG. The use of intravenous NTG also led to an improvement in documented ischemic episodes.[41] Kaplan and Wells described the treatment of postintubation myocardial ischemia as diagnosed by large "V" waves on the PCWP tracing and by ST-segment depression with the use of NTG.[36] The beneficial effects of NTG can be enhanced by maintaining blood pressure in a normal range.[18,30,32,64] The addition of phenylephrine to maintain blood pressure during infusion of NTG for treatment of ischemia and infarction was shown by Borer et al to be helpful as long as the patient had good left ventricular function (Fig. 3).[6]

A decrease in infarct size, reduced congestive heart failure, and diminished ischemia recurrence have been found with the use of NTG, however, the studies are too few to be conclusive that NTG should be a routine measure for all patients with acute myocardial infarctions.[1,20,87] The results of trials investigating the effects of intravenous NTG on infarct size show that if treatment is begun soon after symptoms begin (the longest

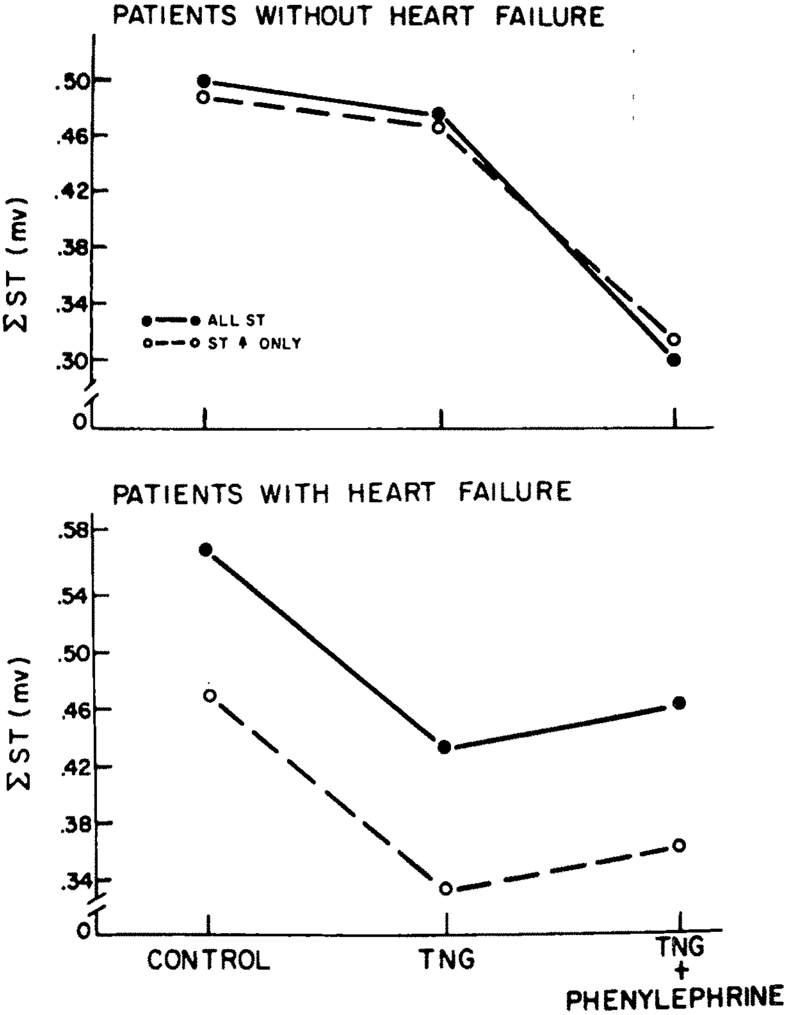

Figure 3. Effects of nitroglycerin alone or with phenylephrine on summation of ST-segment elevation. (*From* Come PC: Reversal by phenylephrine of the beneficial effects of intravenous nitroglycerin in patients with acute myocardial infarction. N Engl J Med 20:1003–1012, 1975; with permission.)

delay in these trials was 10 hours) there is a reduction in infarct size as measured by creatine kinase levels.[9,20,31]

Chiarello et al demonstrated that NTG reduced ST-segment elevation in patients with anterior MI where nitroprusside (NTP) increased ST-segment elevation and, therefore, postulated that NTP caused a "coronary steal" phenomenon.[13] Intracoronary administration of NTG has been shown to relieve coronary artery spasm during acute MI.[73] It is important to note that MI is not a homogenous lesion, but there is a central zone of necrotic cells surrounded by ischemic cells that are potentially salvageable.[60]

BETA-ADRENERGIC BLOCKADE

Beta-blockers are effective in treating ischemia and infarction by reducing myocardial oxygen demand ($M\dot{V}O_2$) via antagonism of sympathetic tone.[80] Heart rate is also reduced allowing for greater coronary blood flow. The reduction in $M\dot{V}O_2$ is limited by the increase in LVEDV. Beta blockers can also reduce regional ischemia and improve regional myocardial dysfunction in ischemic myocardial tissue.[92] Beta blockers may change the substrate of the myocardial cell by blocking the catecholamine-induced increase in lipolysis and fatty acid utilization. Metabolism is, therefore, shifted to use of carbohydrates with less oxygen consumed for equal amounts of energy production.[76,80] This may then provide relief to the cell with a limited oxygen supply.

Evidence exists to suggest the presence of β_2-receptors in cardiac muscle cells that may be responsible for some of the inotropic response to isoproterenol on atrial and ventricular muscle.[3] The β_2-receptor may also be responsible for the chronotropic response to isoproterenol in man.[8] Postsynaptic β_2-receptors that may exert a positive feedback on norepinephrine release have been suggested. Thus, the presence of β_2-receptors in the heart may require a closer inspection of the value of β_1-selective versus nonselective blocking agents.[39]

Beta blockers improve the ratio of subendocardial to subepicardial blood flow in both ischemic and normal areas of myocardium in dogs with a coronary occlusion. These drugs may be more appropriate for delaying rather than preventing cell death. They are especially valuable for limiting infarct size in animals subjected to coronary occlusion.[26,49,65] Beta blockers may also improve oxygen delivery to tissues by a rightward shift of the oxyhemoglobin dissociation curve. [90]

Peter et al found that patients treated with propranolol within 4 hours of the onset of symptoms of an uncomplicated MI had significantly lower peak serum creatine kinase levels and less cumulative creatine kinase in plasma than control patients.[78] Those with suspected MIs treated within 4 hours of symptoms had a significantly lower incidence of infarction.[72] Others have confirmed that when given early, beta-blocker therapy can limit enzymatically estimated infarct size.[33] This time frame for institution of beta blockade is 4 to 6 hours.

Esmolol

Selection of a beta blocker is often determined by pharmacokinetic parameters, and β_1 or β_2 selectivity. Esmolol is rapidly metabolized and cardioselective and, therefore, is ideally suited for intraoperative use. During periods of surgery that require rapid attenuation of hemodynamic stress, it can be administered intravenously and easily titrated. Multicenter clinical trials have verified its safety during general anesthesia and have shown that it can block the tachycardia and hypertension during induction of anesthesia and tracheal intubation for CABG, carotid endoarterectomy, and other noncardiac surgical procedures.[86] Esmolol exerts its beneficial effects during stress-induced sympathetic activity by blocking adrenergic responses that increase myocardial oxygen demand. In a double-blind randomized study using esmolol at different infusion rates[63] including 100, 200, and 300 μg per kg per minute, and placebo in patients undergoing CABG anesthetized with nitrous oxide, diazepam, pancuronium and oxygen, esmolol-treated patients had significantly decreased heart rate responses to intubation. In patients anesthetized with (high-dose) fentanyl, esmolol significantly attenuated tachycardia associated with surgical stimulation such as sternotomy, aortic dissection, and endotracheal intubation.[23] Esmolol was also shown not to produce a further reduction in heart rate in the unstimulated patients.[23] Others have confirmed the beneficial effects of esmolol in attenuation of hemodynamic responses to surgical stimuli in patients undergoing CABG.[16,71] It has been shown to be less effective in chronically beta-blocked patients, implying no additional benefit.[15]

Hydrolysis of the methyl ester in the molecule by blood esterases located in the cytosol of the red blood cell yields methanol and an acid metabolite that possesses minimal beta-blocking properties.[5,24,96] The esterase is not inhibited by physostigmine, but large doses of esmolol can have an inhibitory effect on human plasma cholinesterase activity.[5,24] The distribution half-life is about 2 minutes and the elimination half-life is about 9 minutes. Esmolol infusions in humans in the range of 25 to 300 μg per kg per minute produce linear dose-related hemodynamic effects.[58] Because of its cardioselectivity, it produces minimal increase in specific airway resistance and sensitivity to drug-induced bronchostriction in asthmatics.[95]

Esmolol has been shown to reduce myocardial infarction size and improve recovery of myocardial function after reversible ischemia in experimental models.[44] In patients with acute myocardial infarctions and left ventricular dysfunction, cardiac conduction problems, borderline to low blood pressure, and bronchospastic disease, esmolol may be especially useful since the beta blockade can be rapidly terminated by simply discontinuing the drug.

In the presence of hepatic and/or renal dysfunction, the drug can be safely used because of its dependence on cytosolic enzymatic degradation. Interactions with succinylcholine, morphine, digoxin, and warfarin have been shown to be clinically insignificant.[5,24]

In patients with coronary artery disease the development of a supraventricular tachycardia is poorly tolerated. Esmolol has been shown to be safe and effective for control of the ventricular response. The most frequent adverse effect was hypotension, which resolved within 30 minutes of discontinuation. Those postoperative patients prone to develop hypotension had higher baseline heart rates and a lower baseline blood pressure.[97]

Lange and colleagues[49] studied the effects of esmolol on infarct size and segmental wall dynamics of reperfused myocardial infarcts in anesthetized dogs. After 3 hours of occlusion of the LAD followed by reperfusion, esmolol-treated dogs demonstrated significantly less tissue necrosis compared with controls. Functional deterioration on reperfusion was noted only in placebo-treated dogs. Other studies in dogs have confirmed esmolol's ability to reduce infarct size when infused before and during coronary occlusion.[101] In another experimental study[50] involving open chest dogs with stunned myocardia (brief periods of transient coronary occlusion followed by reperfusion) esmolol in doses of 100 to 150 μg per kg per minute infused before and during coronary occlusion was found to have beneficial hemodynamic effects. During reperfusion, recovery of subendocardial wall motion represented by systolic shortening was significantly greater in esmolol-treated dogs compared with controls. This implied that esmolol accelerated postischemic recovery of reperfused stunned myocardium.

By virtue of its ability to control postoperative hypertension, esmolol may prevent perioperative myocardial ischemia and infarction. Esmolol when compared with nitroprusside was found to be safe and effective.[25] It did not decrease diastolic blood pressure to the same extent as did nitroprusside. It decreased heart rate but did not decrease the partial pressure of oxygen and oxygen saturation as seen with sodium nitroprusside.

CALCIUM CHANNEL BLOCKERS

These drugs also serve as a major treatment modality for ischemia and infarction in the perioperative period. They (1) decrease myocardial oxygen demand by decreasing afterload and improving diastolic relaxation of the heart; (2) improve myocardial blood flow by direct coronary vasodilatation and may improve coronary collateral blood flow; and (3) have a cardioprotective effect during transient myocardial ischemia.[52,84]

Myocardial ischemia and subsequently decreased high-energy phosphate and ATP levels lead to a large influx of extracellular calcium through dysfunctional calcium channels and produce pathologic cellular calcium overload and organelle destruction (Fig. 4).[83] Myocardial ischemia can increase the resting membrane potential in ventricular tissue so that the action potential and electrophysiologic properties resemble nodal tissue with automaticity characteristics and reduced conduction velocity, which lead to automatic foci and reentry phenomona.[22] Therefore, calcium channel blockers, which do have measurable electrophysiologic effects on nodal tissue, can decrease automaticity and conduction velocity, increase refractory period, and thereby prevent ventricular dysrhythmias produced by ischemia.[85]

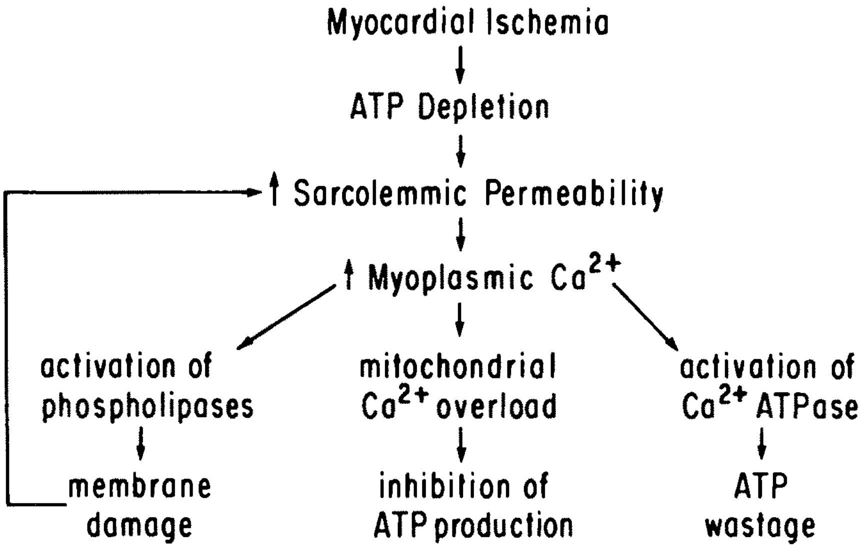
Myocardial Ischemia
ATP Depletion
↑ Sarcolemmic Permeability
↑ Myoplasmic Ca2+
activation of phospholipases
membrane damage
mitochondrial Ca2+ overload
inhibition of ATP production
activation of Ca2+ ATPase
ATP wastage

Figure 4. ATP depletion from myocardial ischemia results in a massive Ca^{++} influx, which further augments ischemic tissue injury.

Calcium antagonists, verapamil, nifedipine, and diltiazem have been shown to reduce the severity of ischemia as well as infarct size.[29,43,70,81] In animals they may exert their anti-ischemic effect by blocking calcium entry into ischemic cells and thereby lower their $M\dot{V}O_2$ and reduce the ischemia-induced reduction of high-energy phosphates. The calcium channel blockers probably do not work on irreversibly injured cells. These agents are probably most beneficial when administered prophylactically or early in the course of ischemia.[12,43,57,70] However, two multicenter prospective trials in evolving myocardial infarction could not show a reduction in infarct size by the early use of nifedipine.[67,93] There has also been conflicting results with diltiazem used in an animal model of acute MI.[42,53]

Experimental evidence demonstrates a protective effect of calcium channel blockers during brief periods of ischemia. However, they are less effective during prolonged ischemia. When given to animals before or soon after the onset of ischemia, nifedipine reduces the extent of irreversible myocardial injury; verapamil reduces ischemic contracture, mitochondrial calcium overload, and infarction size; and diltiazem reduces reperfusion injury.

For the treatment of coronary spasm, calcium channel blockers are the drugs of choice. They also serve a prophylactic function.[17]

Interest is now focusing on the dyhydropyridine calcium channel antagonist nicardipine. It is a potent vasodilator that is not associated with the degree of myocardial depression noted with other calcium channel blockers at pharmacologic doses, and according to Lambert et al[48] this drug may even increase the indices of the myocardial contractile state independent of its systemic vasodilator properties. It is available in intravenous form.

METABOLIC INTERVENTION

Ischemia impairs fatty acid oxidation, so that glucose becomes the primary energy source.[74] In ischemic dogs, oxidative phosphorylation and cardiac function are improved by the infusion of glucose-insulin-potassium (GIK).[11] The benefits of GIK may be due to (1) increases in contractility secondary to the hyperosmolar activity of the glucose solution[100]; (2) a decrease in the concentration and myocardial uptake of circulating free fatty acids that leads to a decrease in $M\dot{V}O_2$; (3) restoration of the intracellular potassium concentration; and (4) decreases in the incidence of serious ventricular dysrhythmias.

In the canine model of coronary occlusion, GIK started 30 minutes after occlusion and maintained for 24 hours decreased the extent of myocardial necrosis.[61] GIK use in the baboon after acute coronary occlusion preserves myocardial energy stores with greater amounts of ATP, creatine phosphate, and glycogen in the ischemic zones of treated than in untreated animals.[75] In a nonrandomized study,[28] an infusion of glucose 300 g, insulin 50 U, and KCL 80 mEq in 1,000 ml of water at a rate of 1.5 ml per kg per hour appeared to reduce mortality and improved hemodynamics with decreased asynergy in the ischemic zone.[28,88] However, no definitive effect on enzymatically measured infarct size or long-term mortality has been described in a prospective controlled study.

OXYGEN-DERIVED FREE RADICAL SCAVENGE

Ishemic tissue generates oxygen-derived free radicals. The three principle ones are the superoxide anion (O_2-), hydrogen peroxide (H_2O_2), and hydroxyl (OH^-) group. These oxygen radicals contribute to causing the cellular damage of ischemia. They promote peroxidation of cell membranes and contribute to cell death.[27] They may also cause irreversible injury by acting on mitochondria and sarcoplasmic reticulum. The free radical scavengers, superoxide dismutase and catalase, prevent ischemia-induced loss of calcium sequestration by the sarcoplasmic reticulum[45] and preserve mitochondrial function.[89] After brief ischemia, free radical scavengers improve the rate of recovery of myocardial function[34,99]; this implies that free radicals play a role in the postischemic depression of myocardial function.[69,82] On reperfusion of ischemic tissue with oxygen there is an increase in production of oxygen-derived free radicals, and it may be these substances that limit the benefits of reperfusion.

In an effort to limit infarct size, the combination of thrombolytic treatment and free radical scavengers may prove to be an effective regimen when instituted early or before an ischemic episode.

INTRA-AORTIC BALLOON PUMP

As a method of treatment of ischemia and infarction the intra-aortic balloon pump (IABP) has been used to (1) stabilize patients for emergency coronary surgery; (2) control the hemodynamic deterioration of the patient during high-risk percutaneous transluminal coronary angioplasty; (3) prepare patients for emergency noncardiac surgery with hemodynamically unstable angina; and (4) augment cardiac pump function after massive myocardial infarction or cardiopulmonary bypass with low cardiac output.

By producing favorable decreases in myocardial O_2 demand and increases in myocardial oxygen supply, this device has become an important adjunct to pharmacologic therapy. No definitive information is available indicating that IABP alters the prognosis of patients with uncomplicated MI. However, Leinbach et al[51] found an immediate persistent fall in ST-segment elevation when IABP was used within 6 hours in patients with anterior MI who had preservation of R waves, good ventricular function, and in whom the LAD was not totally occluded. In view of a lack of convincing data for infarct size reduction and because of finite complications associated with its use, it should be reserved for those with refractory ischemia and for the hemodynamically compromised.

SUMMARY

While the role of nitrates, beta blockers, and calcium channel blockers in the treatment of myocardial ischemia and infarction has been shown, they are not complete therapies. They must be instituted early, often before ischemic episodes, and they cannot completely control injury to cells already damaged or those injured by reperfusion. Future therapies involving metabolic substrate manipulation, prostaglandins, or free radical scavengers need to be further investigated.

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Cardiologic Reperfusion Treatment for Acute Myocardial Infarction

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The treatment of acute myocardial infarction has undergone revolutionary changes in recent years since the introduction of thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA). Previous conventional treatment for acute myocardial infarction consisted of bed rest combined with prophylaxis and treatment of complications such as arrhythmias or circulatory failure in a coronary care unit.

Reperfusion therapy was initially introduced in 1976 by Chazov et al,[4] who administered intracoronary streptokinase into a totally occluded coronary artery during acute myocardial infarction and established reperfusion. Rentrop et al[27] subsequently demonstrated the effectiveness of an intracoronary infusion of streptokinase in restoring coronary blood flow during acute myocardial infarction. Since then, acute intervention by both pharmacologic and mechanical reperfusion techniques has become widely used during acute myocardial infarction; these approaches have included both intracoronary and intravenous infusion of various thrombolytic agents such as streptokinase, urokinase, and tissue-type plasminogen activator (tPA), PTCA alone, or the combined use of PTCA and thrombolytic agents.

The rationale for limiting infarct size by reperfusion treatment is based on evidence that residual left ventricular function is the most important prognostic factor following acute myocar-

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dial infarction.[20] There is an exponential relationship between left ventricular ejection fraction and prognosis (Fig. 1). Patients with a normal ejection fraction have a greater than 95 per cent 3-year survival rate. In contrast, those with an ejection fraction less than 20 per cent had 30 to 75 per cent 3-year survival rates depending on the number of diseased coronary vessels. The goal of acute intervention during myocardial infarction is to establish early reperfusion in order to limit myocardial infarct size and preserve left ventricular function, so that the long-term prognosis of the patient may improve following acute myocardial infarction.

PATHOPHYSIOLOGY OF ACUTE MYOCARDIAL INFARCTION

The role of thrombus in acute myocardial infarction was controversial until recently when several studies identified thrombus formation as a cause of myocardial infarction rather than as a result of a total occlusion. DeWood et al[7] demonstrated a high incidence of thrombus among patients with acute transmural myocardial infarction. Patients who were evaluated

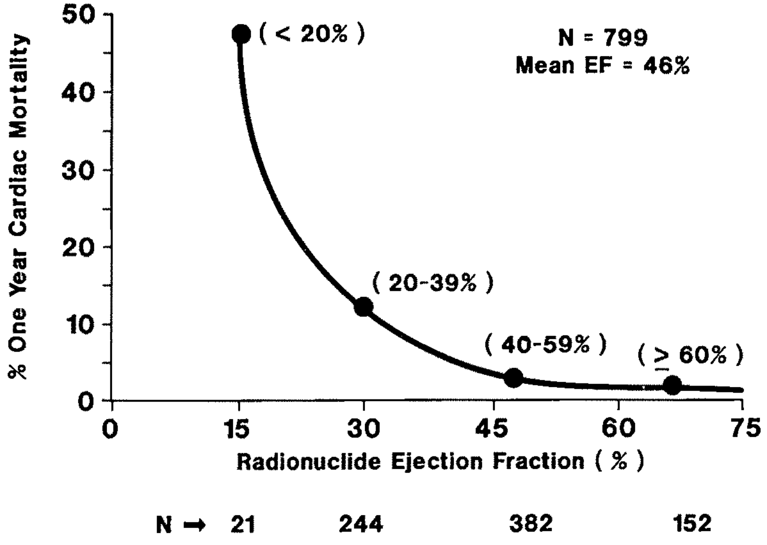


Figure 1. Cardiac mortality rate in four categories of radionuclide ejection fraction (EF) determined before discharge. N denotes the number of patients in the total population and in each category. Of 811 patients in whom the ejection fraction was recorded, 12 were lost to follow-up during the first year after hospitalization. (*From* The Multicenter Postinfarction Research Group: Risk Stratification and Survival after Myocardial Infarction. N Engl J Med 309:331–336, 1983; with permission.)

within 4 hours after the onset of chest pain had a high incidence (87 per cent) of total occlusion of the infarct-related artery during emergency cardiac catheterization; the presence of thrombus was documented in a significant number of patients by either coronary arteriography or inspection of the coronary artery during bypass surgery. Thrombus generally forms on a preexisting atherosclerotic plaque, but the mechanism of its acute formation is not clear. One hypothesis is that an atherosclerotic plaque ruptures, exposing thrombogenic elements to blood and leading to platelet aggregation and localized coagulation.

Following acute coronary occlusion, myocardial necrosis starts in the core of the ischemic zone and then spreads toward the border zone (wavefront phenomenon). In an experimental animal model, Reimer et al[24] demonstrated that myocardial necrosis starts within 30 minutes after occlusion of the coronary artery; the area of necrosis involves approximately two thirds of the jeoparidized region within 3 hours and myocardial infarction is completed after 6 hours of occlusion (Fig. 2). This process could be altered by reperfusion, which salvages myocardium that would otherwise have undergone irreversible myocardial necrosis. Since the extent of myocardial necrosis

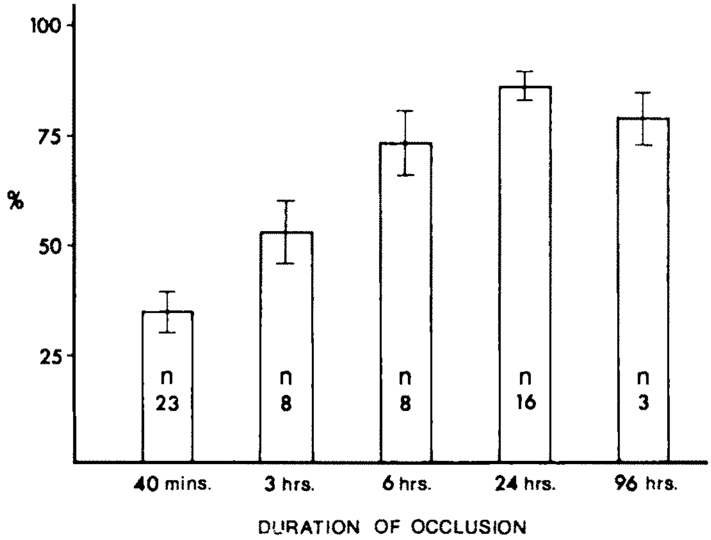


Figure 2. Per cent of myocardium in the distribution of the circumflex coronary artery showing histologic evidence of necrosis following temporary coronary occlusion ranging from 40 minutes to 96 hours in 58 dogs. (*From* Reimer K, Lowe J, Rasmussen M, et al: Myocardial infarct size versus duration of coronary occlusion in dogs. Circulation 56:786–794, 1977; with permission.)

depends largely on the duration of the coronary occlusion, early intervention is necessary to salvage myocardium.

Although reperfusion prevents further myocardial necrosis, there may be adverse reactions from the reperfusion, including hemorrhage into the myocardium or reperfusion injury. Reperfusion injury is poorly understood at the present time. It may be related to the toxic effect of oxygen-free radicals formed in the infarcted area following reperfusion. The clinical significance of reperfusion injury is not clear and further studies are necessary to evalute this phenomenon.

Recovery of left ventricular function following reperfusion has been observed in both experimental and clinical studies. The recovery of myocardial contractility may not occur immediately but may be delayed for prolonged periods; Braunwald and Kloner[1] introduced the term "stunned myocardium" to describe this delayed recovery. Even brief occlusion of the coronary artery without myocardial necrosis may result in depressed contractility for several days, along with prolonged reduction of ATP concentration in the ischemic myocardial cells. In dogs, delayed recovery of function following 2 hours of occlusion has been reported.[36] In this case, some necrosis occurred in the ischemic zone but severely damaged cells were also present. Stack et al[35] showed significant improvement of function at 1 week but not within 24 hours in jeopardized regions among patients who had successful sustained reperfusion following acute myocardial infarction. Therefore, it is important to evaluate left ventricular function not immediately after reperfusion but at least 1 week following acute myocardial infarction.

REPERFUSION TREATMENT

Spontaneous reperfusion may occur without any specific treatment as demonstrated by DeWood et al.[7] Among patients who were evaluated within 4 hours of the symptoms, a majority (87 per cent) had a total occlusion of a coronary artery documented by coronary angiography. The incidence of total occlusion decreased with duration after the onset of chest pain; 68 per cent between 6 to 12 hours and 65 per cent between 12 to 24 hours after the onset of chest pain. However, spontaneous reperfusion occurs in such a small number of patients, thus, it is necessary to have definite approaches to establishing reperfusion. These include intracoronary or systemic thrombolytic therapy, emergency PTCA, combined thrombolytic therapy and PTCA or emergency coronary artery bypass surgery.

Thrombolytic Therapy

The rationale for using thrombolytic therapy during acute myocardial infarction is that fresh thrombus formation is the major cause of acute occlusion. Thrombolytic therapy can be administered either selectively via intracoronary infusion or systemically intravenously. In an early experience, thrombolytic agents were more frequently given by the intracoronary route, but recently systemic thrombolytic therapy by intravenous infusion has become a widely accepted method. The main advantage of the intravenous method is that treatment can be initiated as soon as the patient is evaluated. In addition, it does not require any special equipment or an experienced coronary angiographer and can be administered in the emergency room of a community hospital. Early treatment is the key factor since duration of occlusion is the important determinant of myocardial salvage and the reperfusion rate is higher in patients with shorter duration of chest pain prior to treatment.

Currently, three different thrombolytic agents are clinically available: streptokinase, urokinase, and tPA. At present, only streptokinase and tPA are approved by the Food and Drug Administration for the treatment of acute myocardial infarction. Anisoylated plasminogen streptokinase activator complex (APSAC)[15] and pro-urokinase[6] are under investigation as the next generation of thrombolytic agents.

Each thrombolytic agent has a different mechanism of action. Streptokinase induces clot lysis by forming a complex with plasminogen that converts to plasmin. Plasmin has a potent action to lyse existing thrombus. Urokinase, in contrast, activates plasminogen directly to plasmin. Neither agent is clot-specific and both cause significant systemic lytic states with depletion of circulating fibrinogen. In contrast, tPA is a clot-specific thrombolytic agent with a low affinity for circulating plasminogen and a high affinity for fibrin. Plasminogen and tPA selectively accumulate on the surface of a thrombus where tPA activates plasminogen to plasmin. Because plasmin production by tPA is mostly confined to the thrombus site, derangement of systemic coagulation system is miminal. In constrast to urokinase or streptokinase, which have longer half-lives and induce prolonged systemic fibrinogen depletion, tPA has a short half-life and relatively less fibrinogen depletion with the usual dose.

The reperfusion rates achieved with each thrombolytic agent are different. The reperfusion rate with 1.5 million units of intravenous streptokinase ranges from 10 to 62 per cent, with an average of about 45 per cent.[25] The reperfusion rate with tPA is generally higher than streptokinase and ranges from 62 to 79 per cent.[5,37–39] In the Thrombolysis in Myocardial Infarction Trial (TIMI) I trial,[5] in which initial coronary occlusion was documented angiographically prior to initiation of therapy, the reperfusion rate 90 minutes following treatment was 31 per cent with intravenous streptokinase and 62 per cent with intravenous tPA. In the European Cooperative Study, the patency rate was 70 per cent for tPA and 56 per cent for streptokinase.[39] In the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) I trial without initial angiographic documentation, the infarct-related artery patency 90 minutes following the infusion of tPA was 79 per cent.[37] These studies indicate that systemic thrombolytic therapy enhances clot lysis and can effectively achieve reperfusion during acute myocardial infarction. Among currently available agents, tPA seems to have the highest reperfusion rate although a significant number of patients given tPA failed to reperfuse.

The most serious adverse effect associated with thrombolytic therapy is bleeding complications. Although tPA has less effect on fibrinogen levels than streptokinase, the frequency of bleeding complications is similar in both groups. Most bleeding complications are associated with the peri-access site (the site of catheterization). Serious bleeding complications other than peri-access bleeding are rather infrequent, but complications such as intracranial or gastrointestinal hemorrhage are potentially lethal. The incidence of intracranial hemorrhage or stroke with 1.5 million units of intravenous streptokinase ranges from 0.2 to 1.0 per cent.[9,13,33,41]

In the pilot study of the TIMI II study, the incidence of intracranial hemorrhage among patients who received 150 mg of tPA was 1.6 per cent. Accordingly, the tPA dosage was decreased to 100 mg intravenously in the later phase of this study and the incidence of intracranial hemorrhage subsequently decreased to 0.6 per cent.[2]

All thrombolytic therapy has the potential hazard of major bleeding complications, so careful screening of patients prior to administration is essential. When the patient is evaluated for possible thrombolytic therapy during acute myocardial infarction, a careful history should be obtained. The absolute and relative contraindications for thrombolytic therapy are listed in Table 1. Thrombolytic therapy should not be administered to patients with absolute contraindications in any circumstances. The risk of serious complications in patients with a relative

Table 1. *Guidelines for the Selection of Patients for Thrombolytic Therapy During Evolving Acute Myocardial Infarction*

- Contraindications
  - Active internal bleeding
  - Recent (2 weeks) major surgery or organ biopsy
  - Recent (4 weeks) gastrointestinal or genitourinary bleeding
  - History of cerebrovascular accident
  - Recent (4 to 6 months) intracranial or spinal surgery or trauma
  - Intracranial neoplasm, aneurysm or AV malfunction
  - Uncontrolled hypertension: severe
  - Bleeding diathesis
- Relative contraindication
  - Hypertension (diastolic ≥110 mm Hg; systolic ≥180)
  - Advanced liver disease
  - Advanced renal failure
  - Diabetic retinopathy
  - Advanced age (≥75 years old)
  - Prolonged cardiopulmonary resuscitation (>10 min)
  - Severe trauma within the past 6 months that may predispose the patient to intracranial, intrathoracic, intra-abdominal, or retroperitoneal bleeding

contraindication is high, and use of thrombolytic therapy needs to be avoided if possible. In general, these patients should undergo emergent catheterization and PTCA rather than thrombolytic therapy.

In summary, thrombolytic therapy should be administered early to patients with evolving acute myocardial infarction. Each patient needs to be carefully evaluated for potential benefits and risks in order to maximize effectiveness and minimize potentially fatal bleeding complications. Its use in the surgical patient who develops an acute infarction has not been investigated.

Percutaneous Transluminal Coronary Angioplasty

PTCA during acute myocardial infarction was first reported in 1982[19] and since then it has become one of the major approaches to achieving reperfusion during acute myocardial infarction. Despite thrombolytic therapy, the infarcted artery remains occluded in approximately 25 to 30 per cent of patients. In addition, most patients successfully reperfused by thrombolytic therapy have a significant residual stenosis that predisposes to recurrent ischemia or reocclusion during the hospital stay.[11]

In the early stages of experience, popular approaches were either direct PTCA without thrombolytic therapy or combined intracoronary streptokinase infusion and PTCA. The success rate was 72 to 100 per cent.[33] In a study from Duke University Medical Center, 216 patients with acute myocardial infarction were treated with an intravenous infusion of 1.5 million units of streptokinase followed by emergent PTCA.[33] Persistent coronary perfusion was achieved in 90 per cent while 87 per cent had successful PTCA with a residual stenosis ≤50 per cent. The in-hospital reocclusion rate was 11 per cent (symptomatic reocclusion 7 per cent, silent reocclusion 4 per cent). In a randomized study, O'Neill et al[21] evaluated the role of emergent PTCA for acute myocardial infarction; reocclusion occurred in 15 per cent of patients treated with intracoronary streptokinase alone and in 7 per cent with PTCA alone. As indicated by these studies, PTCA can be performed safely and effectively during acute myocardial infarction, however, certain limitations need to be noted. Although the success rate for emergency PTCA during acute myocardial infarction is high, it is still significantly lower than for elective PTCA (87 versus 94 per cent).[22] In addition, the reocclusion rate is higher following emergent PTCA than elective PTCA (9 versus 3 per cent).[22]

The efficacy of PTCA was recently examined in a randomized trial. The TAMI I study compared early and late PTCA following successful reperfusion by tPA.[37] One hundred ninety-seven patients were randomized to either emergency PTCA or elective PTCA. Among patients with emergent PTCA, the success rate was 86 per cent while 7 per cent required emergency coronary artery bypass grafts for failed PTCA. In the late PTCA group, the success rate was 92 per cent. In addition, a significant number of patients had marked improvement of residual stenosis without PTCA at 1 week following acute myocardial infarction. Episodes of recurrent ischemia were more frequently observed in the elective PTCA group than in the emergent PTCA group (16 versus 5 per cent), but the incidence of reocclusion was similar in both (13 versus 11 per cent).

The major role of emergent PTCA in the thrombolytic era may be found in the patient with total occlusion that has failed to reopen with thrombolytic therapy. PTCA can achieve reperfusion and improve the residual stenosis, and theoretically, will salvage myocardium and improve survival. In the TAMI I trial, emergent PTCA was performed in patients who had persistent total occlusion despite tPA treatment.[3] Seventy-five per cent of patients had successful PTCA, 16 per cent were reperfused with significant residual stenosis (greater than 50 per cent) and 10 per cent had failed PTCA. Disappointedly, 29 per cent of patients who had successful initial PTCA or reperfusion reoccluded during subsequent hospitalization. In the TAMI II trial, in which combined intravenous tPA and urokinase were used, the outcome of emergent PTCA for total occlusion despite thrombolytic therapy was more encouraging.[34] The incidence of reocclusion following PTCA was only 5 per cent with this approach. In addition, in contrast to the TAMI I experience, there was significant improvement of both regional wall motion and left ventricular ejection fraction. This preliminary result suggested that the type of thrombolytic agent may be an important factor when patients need emergent PTCA for totally occluded vessels despite thrombolytic therapy.

In summary, emergency PTCA can be performed safely during acute myocardial infarction with a relatively high success rate. However, the success rate is lower than in elective PTCA and the reocclusion rate is higher. Therefore, the patient may undergo elective PTCA rather than emergent PTCA if reperfusion can be established with thrombolytic therapy. Emergent PTCA remains the only available method to establish reperfusion in patients in whom thrombolytic therapy fails. The incidence of reocclusion following emergency PTCA for a totally occluded vessel is high in patients treated with tPA alone. Other thrombolytic agents or combined use of agents may be necessary to reduce the incidence of reocclusion following emergency PTCA.

BENEFICIAL EFFECT OF REPERFUSION

The benefit and efficacy of reperfusion treatment can be evaluated by determining either alteration of prognosis or salvage of myocardium. In the last several years, many randomized studies as well as observational studies have been performed, and these studies provide us with the opportunity to evaluate reperfusion therapy.

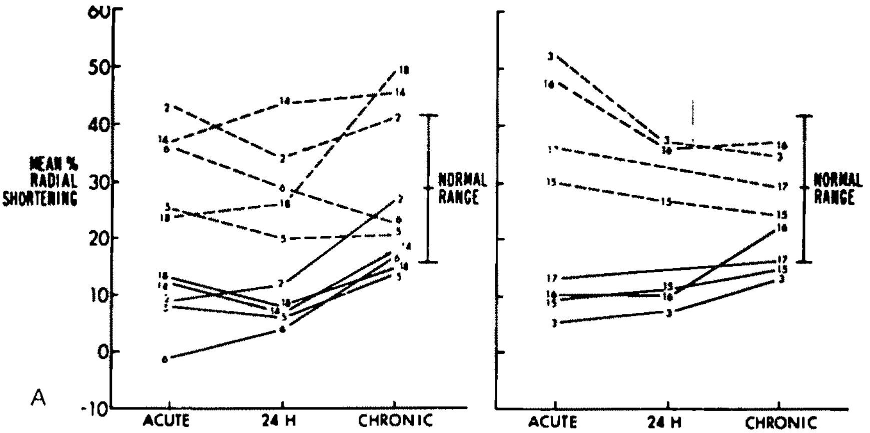
Left Ventricular Performance

One method of evaluating reperfusion treatment is by estimating the amount of myocardium that is salvaged. Salvage of myocardium can be accurately assessed in experimental animal models where both infarct size and risk zone can be measured. In humans, these measurements cannot be adequately obtained; thus, it is necessary to measure myocardial salvage indirectly. One widely used method is to measure recovery of left ventricular function following intervention. Left ventricular function during the acute phase is used as a baseline to identify the risk area and is then compared with function at the subsequent convalescent stage.

While left ventricular ejection fraction has been used to evaluate reperfusion treatment, many studies have failed to show significant improvement of left ventricular ejection fraction following intervention.[16,29,35] Left ventricular ejection fraction is affected by many factors including preload, afterload, and contractility. During the acute stage of a myocardial infarction, despite significantly depressed regional wall motion in the infarcted segments, overall left ventricular ejection fraction may be maintained due to compensatory movement of noninfarct segments, probably in response to elevated catecholamine levels. In the recovery phase, the degree of compensatory movement may decrease while movement in the infarcted region improves significantly, resulting in an unchanged ejection fraction (Fig. 3). Therefore, it is necessary to evaluate not only ejection fraction but also regional wall motion in order to assess myocardial salvage with accuracy.

Compared with the inconsistent results of left ventricular ejection fraction following reperfusion,[16,23,26,29] there is a consistent finding that successful restoration of coronary blood flow is associated with significant improvement of regional function. This has been observed for all modes of intervention—intracoronary or intravenous thrombolytic therapy, emergency PTCA, or combined therapy. Stack et al observed a significant improvement of function in jeopardized regions among patients who had successful reperfusion but not among those who had no reperfusion (Fig. 3).[35]

Several factors influence the degree of improvement of regional wall motion following reperfusion; these are residual stenosis, duration of chest pain prior to reperfusion, and the presence or absence of collateral arteries. Usually, acute intervention is attempted only among patients whose duration of chest pain is less than 6 hours. This is based on animal studies that demonstrated that most infarctions are complete within 6 hours and that salvage of myocardium depends on the time to reperfusion after coronary occlusion. In human studies, similar findings have been observed. Koren et al[18] showed that both ejection fraction and regional wall motion were better in patients with pain duration less than 1.5 hours prior to intravenous streptokinase therapy than in those with pain longer than 1.5 hours. The TIMI trial also demonstrated the relationship between time to reperfusion and functional recovery of the infarcted segment.[30] However, there is significant variation in each individual patient, and the functional recovery of the left ventricle may occur even in those with chest pain lasting longer than 6 hours.[12]



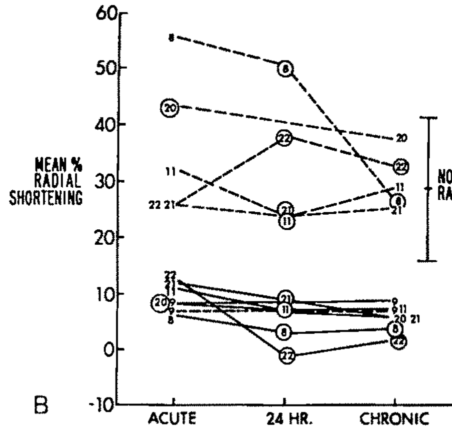


Figure 3. (*A*, left) Per cent radial shortening (RS) in all patients with acute and chronic catheterization studies who were initially reperfused and who showed a significant (≥5 per cent) improvement in angiographic ejection fraction between the acute and chronic study. Changes in the percentage radial shortening in the jeopardized region are shown using solid lines while changes in the compensatory region are shown using interrupted lines. The normal range (mean ± 2 SD) for percentage radial shortening in 58 normal patients is shown on the right. (Right) Percentage radial shortening in patients with acute and chronic catheterization studies who were initially reperfused and who showed no change or a decrease in the ejection fraction between the acute and chronic studies. (*B*) Percentage radial shortening in all patients with acute and chronic catheterization studies who were not reperfused during the acute study or who later reoccluded after initial recanalization. A circle around the patient number indicates that the infarct-related vessel was open at the end of the study. Changes in the percentage radial shortening in the jeopardized region are shown using solid lines while changes in the compensatory region are shown using interrupted lines. (*From* Stack RS, Phillips HR, Grierson DS, et al: Functional improvement of jeopardized myocardium following intracoronary streptokinase infusion in acute myocardial infarction. J Clin Invest 72:84, 1983; with permission.).

The degree of residual stenosis following reperfusion may be an important factor influencing recovery of left ventricular function. Emergency PTCA has been used to decrease residual stenosis following initial reperfusion, and O'Neill et al[21] demonstrated in a randomized trial that more significant improvement in regional wall motion and ejection fraction occurred among patients who had a successful emergent PTCA during acute myocardial infarction than those reperfused by intracoronary streptokinase therapy alone. However, the recent TAMI study, which examined the effect of PTCA following reperfusion by tPA, showed that there was significant improvement of regional wall motion but no difference in the degree of improvement between emergent PTCA and deferred PTCA at predischarge time.

Although emergency PTCA usually establishes reperfusion and improves regional wall motion, its efficacy for a totally occluded vessel despite thrombolytic therapy needs to be evaluated further. In the TAMI study, there was a high incidence of reocclusion following emergent PTCA for totally occluded vessels despite intravenous tPA. In addition, no significant improvement in regional or global left ventricular function occurred even in patients with successful PTCA and sustained patency.[3] In the TAMI II study, in which combined intravenous tPA and intravenous urokinase were administered, preliminary results showed significant improvements in regional wall motion and left ventricular ejection fraction following successful PTCA among those who failed to reperfuse with these agents.[34] Different thrombolytic agents may interact in different ways with PTCA and further study is neccessary to evaluate this effect.

In addition to salvage of myocardium, sustained perfusion to the infarct area may enhance scar formation and prevent expansion of the infarct. A more significant degree of left ventricular dilatation has been observed among patients who had a persistent occlusion of the infarct-related artery than among those with patent arteries.[14] Total arterial occlusion with poor collateral flow has been associated with a high incidence of left ventricular aneurysm formation.[8] Enhancement of scar formation and prevention of infarct expansion with persistent patency of infarct artery may have a favorable effect on long-term prognosis.

In summary, reperfusion therapy during acute myocardial infarction salvages myocardium and significant improvement of regional left ventricular function occurs. Reperfusion should be attempted in the early stages of myocardial infarction since the amount of salvaged myocardium depends on the duration of coronary occlusion.

PROGNOSIS

The main purpose of reperfusion treatment during acute myocardial infarction is to improve prognosis. Randomized studies are essential to evaluate reperfusion therapy adequately. The first randomized trial to show a favorable effect of thrombolytic therapy was the Western Washington trial (intracoronary streptokinase infusion versus placebo).[16] This trial demonstrated a significantly lower in-hospital mortality in the intracoronary streptokinase group (3.7 per cent) than in the control group (11.2 per cent).

The most conclusive evidence for improved prognosis following thrombolytic therapy was documented by the Gruppo Italiano per lo studio della streptochinasi nell Infarto Miocardico (GISSI) trial.[9] This trial included a total of 11,712 patients who had chest pain of less than 12 hours. Patients were randomized to either 1.5 million units of intravenous streptokinase or placebo. Significant reduction (18 per cent) of in-hospital mortality was observed in the group treated with streptokinase. In a subgroup analysis, a statistically significant reduction of mortality was observed only among patients treated within 6 hours of the onset of chest pain. In patients with chest pain lasting less than 1 hour, mortality was reduced from 15.4 per cent (placebo) to 8.2 per cent (streptokinase)—a reduction of 47 per cent (Table 2). Preliminary results from the currently ongoing Second International Study for Infarct Survival (ISIS-2) trial (randomized trial of intravenous streptokinase versus placebo) have also demonstrated a significant reduction in mortality among patients with chest pain duration of less than 4 hours.[13]

Some other randomized trials, such as Streptokinase in Acute Myocardial Infarction (ISAM)[28] have not demonstrated a statistically significant reduction of mortality, probably because of the small number of patients included and the selection of patients at low risk. The pooled data, including more than 5,000 patients from previous randomized studies, also showed a significant reduction of mortality with intravenous streptokinase despite the fact that each individual study failed to show a sig-

Table 2. *Mortality by Hours from Onset of Symptoms*

HOURS	NO.	STREPTOKINASE (%)	CONTROL (%)	P	RELATIVE RISKS
≤1	1277	8.2	15.4	0.0001	0.49
≤3	6094	9.2	12.0	0.0005	0.74
3–6	3649	11.7	14.1	0.03	0.80
6–9	1352	12.6	14.1	NS	0.87
9–12	594	15.8	13.6	NS	1.19

NS, not significant.

nificant reduction.[41] Currently, there is no randomized study to evaluate the effect of reperfusion with tPA on prognosis. Since the reperfusion rate with tPA is higher than streptokinase, it is presumed that mortality should be as low as or lower than the mortality with streptokinase.

In addition to the reduction of in-hospital mortality, the GISSI trial also demonstrated significant sustained benefit over a 1-year period (Fig. 4).[10] The mortality after 1 year was significantly lower in the streptokinase group compared with the placebo group. The Netherlands trial (randomized trial of intracoronary or intravenous streptokinase versus placebo) also demonstrated improvement in survival of patients treated with thrombolytic therapy at 1 year.[31] In contrast, the Western Washington trial (intracoronary streptokinase) did not show a signif-

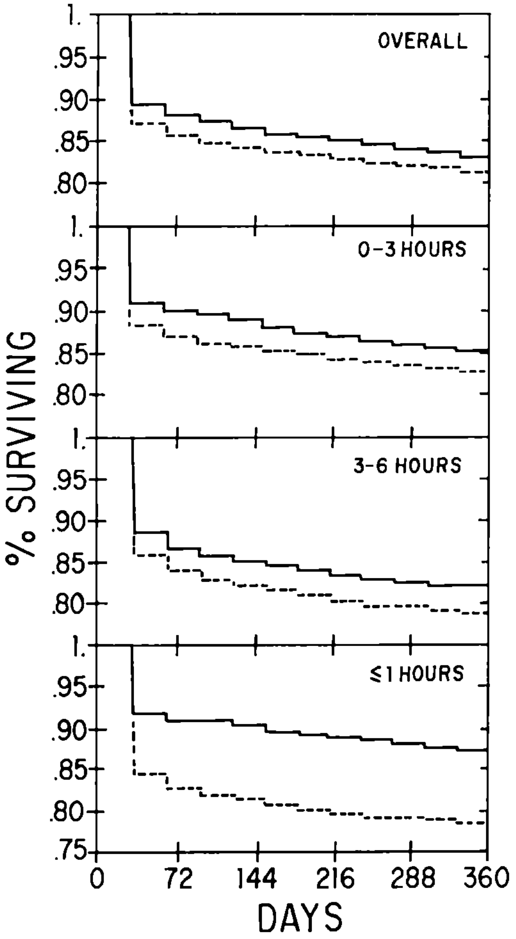


Figure 4. One-year cumulative percentage survival of overall population and survival by hours from onset of symptoms. (*From* Gruppo Italiano Per Lo Studio Della Streptochinasi Nell'Infarto Miocardico (GISSI): Long-term effects of intravenous thrombolysis in acute myocardial infarction: Final Report of the GISSI Study. Lancet II:871–874, 1987; with permission.)

icant reduction of mortality at 1 year.[17] However, when prognosis was examined based on the results of therapy (reperfusion versus no reperfusion) rather than intention to treat, a significantly lower 1-year mortality was observed among patients who had successful reperfusion than among those with sustained total occlusion. Our experience at Duke University Medical Center revealed an in-hospital survival rate of 89 per cent and a 1-year survival rate of 87 per cent among patients who had emergency PTCA for acute myocardial infarction.[32] Only 2 per cent of the patients died in the first year after hospital discharge, a figure considerably lower than those reported for conventionally treated patients in the past (Fig. 5). Even high-risk groups such as patients with cardiogenic shock, old age, and low ejection fraction, which are predictors for in-hospital prognosis, had a very low mortality after hospital discharge. In-hospital survival rates for cardiogenic shock, age greater than 65 years, or ejection fraction of less than 40 per cent, were 58, 75, and 81 per cent, respectively, and 1-year cumulative survival rates were 53, 73, and 77 per cent, respectively.

Although improved mortality with thrombolytic therapy may be related to salvage of myocardium, as suggested by those studies in which improved mortality is time-dependent, persistent perfusion to the infarcted area may be important to prevent cardiac death in the long-term, independent of functional re-

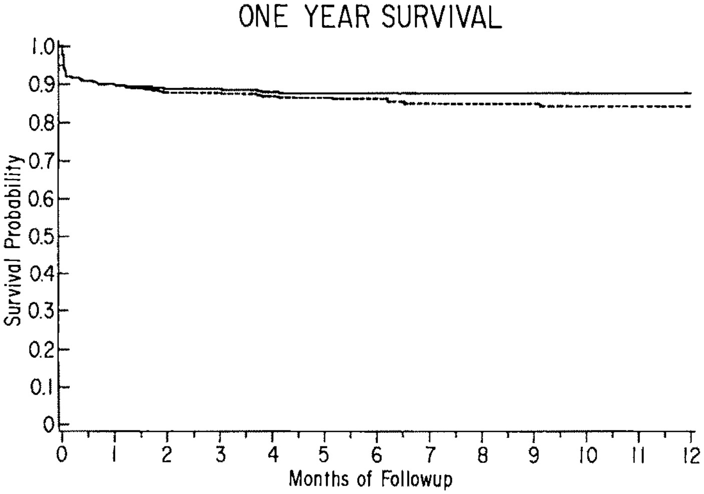


Figure 5. One-year survival (solid line) and 1-year infarction-free survival (interrupted line) following emergency coronary angioplasty for acute myocardial infarction. (*From* Stack RS, Califf RM, Hinohara T, et al: Survival and cardiac event rates in the first year following emergency coronary angioplasty for acute myocardial infarction. J Am Coll Cardiol, in press; with permission.)

covery of myocardium. Our results as well as others revealed a very low mortality rate following discharge among patients with sustained perfusion of the infarct-related vessel. A randomized trial is needed in the future to evaluate the importance of a patent vessel to the infarcted area following acute myocardial infarction.

In summary, recent randomized studies have demonstrated beneficial effects of thrombolytic therapy during acute myocardial infarction. Mortality among patients treated with thrombolytic therapy is significantly lower than among those without treatment. This effect is more significant among patients with shorter duration of chest pain prior to therapy. Reperfusion treatment with intravenous thrombolytic therapy and, if necessary, PTCA should be aggressively used to favorably affect ventricular function and improve prognosis following acute myocardial infarction.

SUMMARY

Reperfusion treatment has become standard during acute myocardial infarction over the last several years. Previous studies have shown that an acute occlusion of the coronary artery due to thrombus formation can be recanalized by thrombolytic agents. Currently, intravenous thrombolytic therapy is widely used. Streptokinase, tPA and, on some occasions, urokinase, have been used for this purpose. tPA has been shown to be particularly effective in achieving reperfusion in approximately 75 per cent of patients. One of the major hazards to using thrombolytic therapy is serious intracranial or internal bleeding complications. Although such complications are relatively infrequent, patients must be carefully screened to exclude those with contraindications when thrombolytic therapy is considered. The alternative method to achieve reperfusion is PTCA. PTCA has been shown to be an effective method of establishing reperfusion during acute myocardial infarction and decreasing residual stenosis. In patients who fail to respond to thrombolytic therapy or those with contraindications to such therapy, PTCA should be considered as the alternative method to achieve reperfusion.

Many studies have demonstrated significant salvage of myocardium by reperfusion therapy and recovery of left ventricular function in the infarct segment. In addition, recent randomized studies have clearly demonstrated beneficial effects on prognosis following thrombolytic therapy. In-hospital mortality

as well as long-term mortality were remarkably reduced with intravenous thrombolytic therapy. Reperfusion by either thrombolytic therapy or PTCA should be considered during acute myocardial infarction to salvage the left ventricle and improve prognosis.

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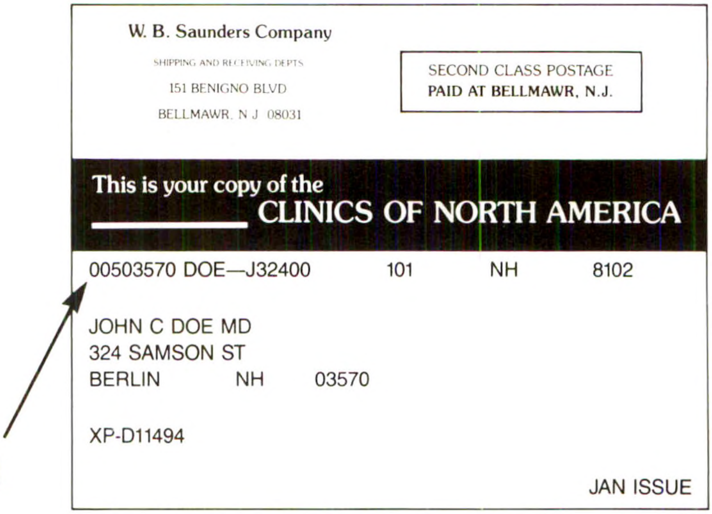

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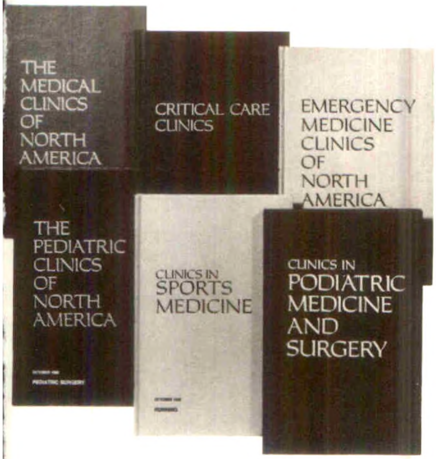
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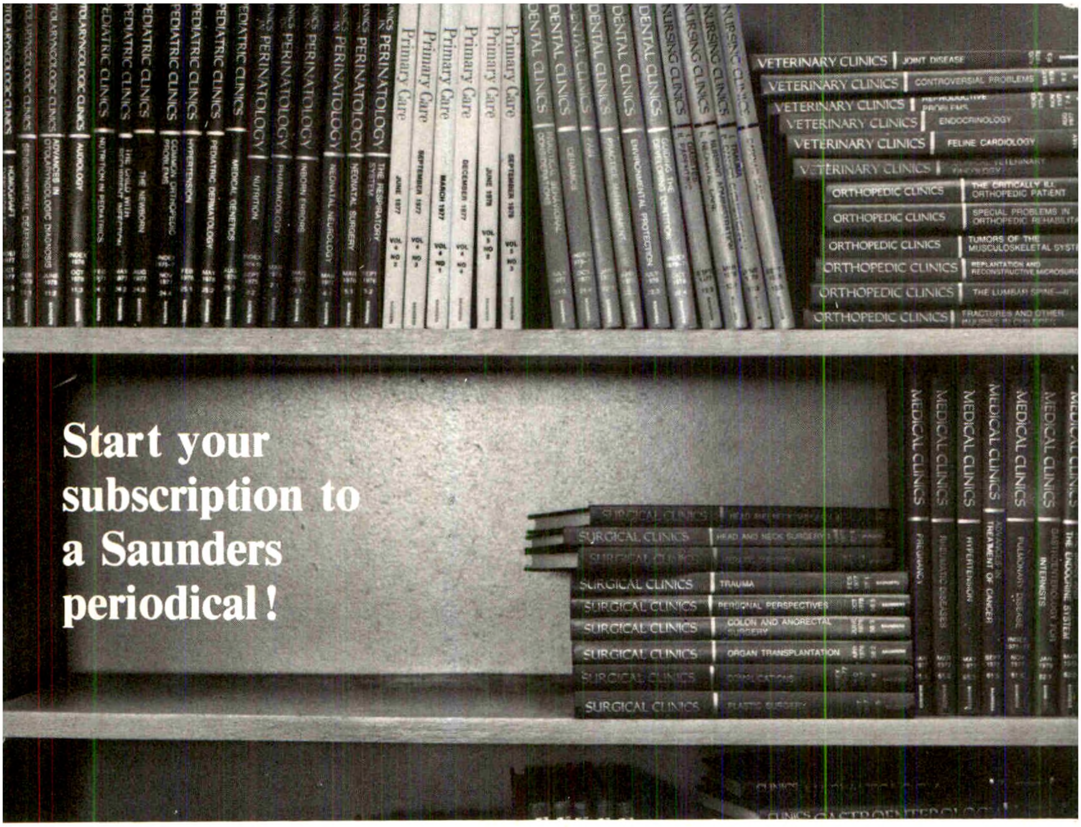

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